DEEPENING THEORETICAL KNOWLEDGE AND EXPLORING THE PROPERTIES OF LOCAL ANESTHETICS

APROFUNDANDO O CONHECIMENTO TEÓRICO E EXPLORANDO AS PROPRIEDADES DOS ANESTÉSICOS LOCAIS

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ABSTRACT: Local anesthetics are indispensable agents in medical practice, offering targeted pain relief while maintaining patient consciousness. Their applications span a wide range of medical fields, including anesthesiology, surgery, and dentistry. Despite their widespread use, the complex pharmacology and potential for adverse effects necessitate a comprehensive understanding of these agents. This narrative review aims to provide an in-depth analysis of the physiology, pharmacology, and clinical applications of local anesthetics. A systematic search was conducted on PubMed, focusing on articles published in English between 2018 and 2023. Local anesthetics have evolved significantly since the first use of cocaine in the late 19th century, with newer derivatives like Lidocaine and Bupivacaine offering improved safety and efficacy. These agents are categorized into aminoesters and aminoamides based on their molecular structure, which also influences their pharmacokinetics and pharmacodynamics. The primary mechanism of action involves the modulation of voltage-gated sodium channels, although the complete mechanism remains an area of active research. Various factors, including lipid solubility, plasma pH, and pKa, influence the drug's onset, duration, and potential for toxicity. Adjuvants like adrenaline can enhance the drug's properties. Local anesthetics are a cornerstone in modern medicine, offering targeted anesthesia with a relatively favorable safety profile. Understanding their complex pharmacology is crucial for optimizing their clinical use. Future research should focus on elucidating the complete mechanisms of action and exploring the potential for new adjuvants to improve efficacy and safety.

Keywords: Local Anesthetics. Pharmacology. Physiology. Mechanism of Action. Pharmacokinetics. Pharmacodynamics. Adjuvants. Toxicity.

INTRODUCTION

Local anesthetics are pharmacological agents that play a crucial role in modern medicine, particularly in areas such as anesthesiology, surgery, dentistry, and pain medicine. These compounds have the unique ability to induce temporary loss of sensitivity in a specific region of the body, making it possible to carry out invasive and diagnostic procedures without causing discomfort to the patient. Furthermore, they are often used in

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conjunction with general anesthetics to provide postoperative analgesia, thus reducing the need for opioid analgesics and their associated side effects. Given their clinical importance, it is imperative to have a comprehensive understanding of the physiology and pharmacology of these agents to optimize their efficacy and safety (Zhang et al., 2022).

The history of local anesthetics dates to the late 19th century when cocaine was isolated from coca leaves and identified as a potent local anesthetic. Carl Koller, an ophthalmologist, was the first to demonstrate the use of cocaine in eye surgery in 1884(Jaichandran, 2013). Procaine, synthesized in 1905 by Alfred Einhorn, emerged as a safer alternative to cocaine (Yoshida et al., 1962). Marketed under the name Novocaine, it quickly gained acceptance in the medical community. After procaine, other ester-type local anesthetics were developed, such as tetracaine and chloroprocaine. However, these compounds had limitations, including a shorter duration of action and potential for allergic reactions. Lidocaine, introduced in the 1940s, was the first amide-type local anesthetic and represented a significant advance in terms of duration of action and safety profile. This led to the development of other amide-type local anesthetics, such as bupivacaine and ropivacaine. With advances in pharmaceutical technology, extended-release formulations have been developed to further extend the duration of anesthesia. The use of adjuvants, such as vasoconstrictors and adrenergic agonists, has become common to increase the efficacy and safety of local anesthetics (Ammar & Mahmoud, 2012).

The purpose of this review is to provide a comprehensive and up-to-date analysis of the physiology and pharmacology of local anesthetics. Specifically, the review aims to elucidate the mechanism of action of these agents on the nervous system, explore their pharmacokinetics and pharmacodynamics, examine the molecular interactions that influence their efficacy and safety, and discuss the use of adjuvants and coadjutants in clinical practice. The focus of this review will be scientific literature published in peer-reviewed journals, including experimental studies, clinical trials and systematic reviews. Clinical guidelines and expert consensus will also be considered to provide a practical perspective on the application of these agents in clinical practice.

METHODOLOGY

This is a narrative review carried out based on articles obtained from PubMed. The descriptors used were ((Physiology) AND (Pharmacology)) AND (Anesthetics, Local). The search covered complete articles in English with a publication period from 2018 to 2023.

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The article selection process was carried out in a double-blind manner using the Rayyan platform for systematic reviews and literature analysis (available at: https://www. rayyan.ai/). Subsequently, the Mendeley platform was used to comprehensively read the selected articles (available at: https://www.mendeley.com/).

RESULTS AND DISCUSSION

Initially, 1,265 relevant articles were identified. After screening, 125 were evaluated using titles and abstracts, and 28 were chosen for full-text examination. After a thorough analysis, 6 articles were selected to be included in the review.

Local anesthetics constitute a pharmacological class designed to alleviate pain while preserving consciousness (Alster, 2013). These agents find applications in a diverse range of medical scenarios, extending from the mitigation of itchiness to the facilitation of intricate procedures such as organ transplantation and antiarrhythmic interventions (Pereira et al., 2020). The genesis of local anesthetics can be traced back to the synthetic derivation of the cocaine molecule in 1902 (Philip et al., 2021). However, the clinical utilization of cocaine is strictly limited to select ophthalmological procedures, owing to its propensity for addiction and its potential to disrupt the Central Nervous System (CNS) (Hoffman, 2010).

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In response to these limitations, a series of compounds structurally related to cocaine have been synthesized to retain anesthetic efficacy while minimizing adverse effects. Lidocaine, introduced in 1947, exemplifies such derivatives and is characterized by its versatile applicability. It can be administered through various routes, including topical application, neuronal blockade infiltration, spinal anesthesia, and epidural anesthesia. Another noteworthy derivative is Bupivacaine, synthesized in 1963, distinguished by its extended duration of action in comparison to Lidocaine (Diaz-Abele et al., 2020).

Local anesthetics are pharmacologically categorized into two primary classes: aminoesters and aminoamides (Sung et al., 2012). Each molecule of a local anesthetic is structurally composed of three distinct functional groups: an aromatic ring conferring lipid solubility, an amine group imparting water solubility, and an intermediate group that influences the anesthetic's duration of action. These structural elements collectively dictate the compound's physicochemical attributes, pharmacokinetic behavior, and toxicity profile. Notably, amides undergo hepatic metabolism, whereas esters are metabolized in the plasma (Gazal et al., 2015).

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The precise mechanism of action underlying local anesthetics remains incompletely understood; however, their primary mode of action is generally accepted to involve the modulation of voltage-gated sodium channels. Upon administration, a local anesthetic traverses the myelin sheath enveloping the neuron and penetrates its phospholipid bilayer (Kostyk et al., 2021). Subsequently, it binds to the voltage-dependent sodium channels, inhibiting sodium influx into the intracellular milieu. This blockade precludes neuronal depolarization and disrupts the propagation of nerve impulses along the afferent pathway of nociceptive pain (Aleman et al., 2015). This contrasts with general anesthetics, which predominantly exert their effects at the neuronal synaptic cleft. In addition to sodium channel blockade, local anesthetics facilitate the efflux of potassium ions from the intracellular environment (Beiranvand et al., 2016). This contributes to increased cellular polarization and renders the cell electrically less conducive to action potential generation, thereby attenuating neural excitability. Furthermore, local anesthetics have been observed to interact with intracellular G protein-coupled receptors, which may influence intracellular calcium regulation (Lv et al., 2022). However, as previously stated, the comprehensive elucidation of the mechanisms governing the action of local anesthetics remains an area of ongoing research.

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The pharmacokinetic and pharmacodynamic properties of local anesthetics are modulated by a myriad of factors, each contributing to the drug's overall efficacy and safety profile (Park et al., 2023). As previously delineated, the aromatic ring within the local anesthetic molecule confers lipid solubility, which in turn influences the rate of penetration through the myelin sheath and the phospholipid bilayer of neurons (Poitelon et al., 2020). Greater lipid solubility not only expedites the onset of action but also prolongs the duration of anesthetic effects. However, the thickness of the myelin sheath serves as a counterbalancing factor; a thicker sheath offers greater protection to the nerve, thereby delaying the anesthetic's access to the phospholipid bilayer (Yoo et al., 2020).

Conversely, the amine group, being water-soluble, enhances the affinity of the anesthetic molecule for its primary site of action, namely the voltage-gated sodium channels. The plasma pH also exerts a significant influence; an acidic environment reduces the anesthetic's binding capacity, while an alkaline milieu promotes protein binding (Mosqueira et al., 2020). The pKa of the anesthetic further modulates its ionization state, thereby affecting its activity. For instance, Lidocaine with a pKa of 7.8 is less ionized and

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exhibits a quicker onset of action compared to Bupivacaine, which has a pKa of 8.1 and is more ionized in acidic conditions (Abendschön et al., 2020).

The intermediate group connecting the aromatic ring and the amine group is associated with the anesthetic's duration of action. A chain length of fewer than three or more than seven carbon atoms in this segment correlates with reduced anesthetic durability. Additionally, the concentration of the anesthetic in the solution impacts its pharmacokinetic properties; elevated concentrations attenuate action potential peaks, increase firing thresholds, diminish impulse conduction, and extend the refractory period (Lauren et al., 2022).

It is noteworthy that sympathetic fibers are more susceptible to blockade and require lower concentrations of anesthetic for effective neuronal transmission inhibition. Lastly, the molecular weight of the anesthetic also plays a role; a higher molecular weight augments the anesthetic's binding affinity to its target site (Mahajan et al., 2014).

Local anesthetics have numerous external factors that can modify their properties, such as adrenaline. When local anesthetics are injected with adrenaline, they increase their durability and even their potency, this is because adrenaline acts as a vasoconstrictor and reduces the systemic absorption of the anesthetic by the body and, consequently, its metabolization (Hsieh et al., 2022) (Choquette et al., 2017) (Korat & Kapupara, 2018).

Regarding the toxicity of local anesthetics, the more acidic the environment, the freer the anesthetic will be in the plasma and the greater its chances of causing systemic toxicity, while the more alkaline the environment, the greater its binding with plasma proteins. Local anesthetics have the capacity to generate neuronal damage if administered in high doses, a mechanism that is not yet well understood, but it is believed to be related to the caspase activation pathway. Not only neuronal damage but also muscle damage if administered intramuscularly. Drugs with more potency and duration, such as Bupivacaine, for example, cause more damage (Gilabert-Estelles & Gilabert-Aguilar, 2014).

Different classes also undergo different metabolisms and have different allergenic potential; Esters are rapidly hydrolyzed in plasma by pseudocholinesterase to the metabolite para-aminobenzoic acid (PABA), which can cause allergies. In the liver, amide-type local anesthetics undergo hydroxylation, metabolism is much slower than plasma hydrolysis and, therefore, amide local anesthetics are more prone to accumulation in the presence of low hepatic blood supply, such as in heart failure, for example (Jeon, 2018). It is worth

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remembering that the administration of adrenaline together with the anesthetic reduces systemic reabsorption and prolongs the effect of the action (Choquette et al., 2017).

The toxicity of local anesthetics can be systemic and/or local and this limits their clinical use. Systemic toxicity manifests mainly in the cardiovascular system and central nervous system. In the cardiovascular system, it slows the nerve conduction of Purkinje Fibers and delays the repolarization of cardiomyocytes. In the central nervous system, they generate non-specific symptoms such as anxiety, dizziness, tinnitus, and vertigo (Otake et al., 2022). Factors such as both respiratory and metabolic acidosis can increase $PaCO_2$ and increase the chance of this toxicity through the dilation of cerebral arteries, which is caused by an increase in $PaCO_2$, increasing cerebral blood flow (Kapetanakis et al., 2011).

Local anesthetics also have anti-inflammatory and immunomodulatory properties, such as reducing the adhesion of polymorphonuclear cells at the site and inhibiting lysosomal enzymes, which will reduce the release of free radicals by macrophages (Shin et al., 2017).

CONCLUSION

The field of local anesthesia has experienced remarkable advances from the discovery of cocaine as the first local anesthetic to the development of amide-type anesthetics and their extended-release formulations. This evolution has allowed greater safety and efficacy in clinical practice, becoming a significant milestone in modern medicine. Pharmacokinetics and pharmacodynamics of local anesthetics are areas of intensive study that provide valuable insights into the mechanisms of action, absorption, distribution, metabolism, and excretion of these drugs. Understanding these aspects is essential for the safe and effective administration of these agents, allowing healthcare professionals to make informed choices about which anesthetic to use, in what dosage and under what conditions. Molecular structure of local anesthetics and their interactions with other drugs are of critical importance. The structure-activity relationship, including the type of bond (ester or amide), the aromatic ring and the amine group, directly influences the potency, duration of action and safety profile of the anesthetic. Furthermore, understanding synergistic and antagonistic interactions with other pharmacological agents can optimize efficacy and minimize risks associated with the use of local anesthetics. The use of adjuvants and co-adjuvants, such as vasoconstrictors and adrenergic agonists, has been shown to significantly improve the efficacy and safety of local anesthetics. These

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agents can prolong the duration of anesthesia, reduce systemic absorption and, consequently, minimize the potential for adverse effects. In terms of clinical applications, local anesthetics are versatile and find use in a variety of settings, from minor surgical procedures and regional anesthesia to chronic pain management. The selection and administration of these agents must be rigorously based on scientific evidence and clinical guidelines to ensure optimal results.

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