

Review Article

The development of local anesthetics and their applications beyond anesthesia

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Abstract: This article reviews the development of classic local anesthetics in the past and presents some recent, new ideas for developing long-acting local anesthetics. It is now widely acknowledged that pain management is a worldwide problem. The use of local anesthetics is one of the most common pain therapies. Local anesthesia includes topical anesthesia, infiltration anesthesia, conduction anesthesia, spinal anesthesia, and epidural anesthesia, etc. Classical local anesthetics mainly consist of aminoesters and aminoamides, the discovery and development of which are based on the discovery of the first local anesthetic drug, cocaine. Different local anesthetics have different clinical applications. Some important properties of clinically used local anesthetics include potency, speed of onset, duration of anesthetic activity, depth of action, and differential blockade, which are related to their physicochemical properties, including lipid solubility, protein binding and pKa, etc. Other factors that also influence anesthetic activity include the dosage of local anesthetic solutions, the addition of a vasoconstrictor to local anesthetic solutions, the injection site, mixtures of local anesthetics, etc. Of course, the side effects of local anesthetics, such as neurotoxicity and cardiotoxicity, should also be of concern. At present, there are two research trends that warrant special attention. One is the development of new high-efficiency and low-toxicity long-acting local anesthetics, which promises to facilitate the occurrence of better local anesthetics. The other is the use of old drugs for new purposes, exemplified by such local anesthetics as anticancer, anti-inflammatory, antimicrobial, and antiarrhythmic anesthetics. This can fully maximize the usefulness of existing drugs. These trends highlight the current directions in research and clinical practice regarding the role of local anesthetics in pain management and beyond.

Keywords: Local anesthetics, pain, aminoesters, aminoamides, long-acting local anesthetics, use of old drugs for new purposes

Introduction

Pain is one of the most common miseries in humans and one of the most unbearable clinical symptoms in patients. Common forms of pain are broadly classified into two categories, including acute pain and chronic pain [1], which cover such specific forms as trauma, postoperative pain, as well as pain caused by osteoporosis, migraine, diabetic neuralgia, back pain, and cancer pain. At present, painkillers mainly include opioids [2] and non-steroidal anti-inflammatory drugs [3]. However, these two types of drugs have some side effects. For example, opioids may cause respiratory depression, addiction, nausea and vomiting, constipation, itchy skin, biliary colic, etc. [4]. Non-

steroidal anti-inflammatory drugs may cause coagulopathy, digestive tract ulcers, liver and kidney dysfunction, etc. [5]. Therefore, the treatment of pain, especially chronic and cancer pain, represents a serious challenge to clinical practice. The Global Burden of Disease Study 2015 showed that the main causes of disability were waist pain and neck pain [6]. In the United States, more than 40% of the population suffers from chronic pain [7]. In middle-income and low-income countries, the prevalence of chronic pain in adults is 33%, and the prevalence of chronic pain in the elderly is 56% [8].

Local anesthetics, which work through a local reversible blockage of sensory nerve impulses, have been used in clinical practice for more

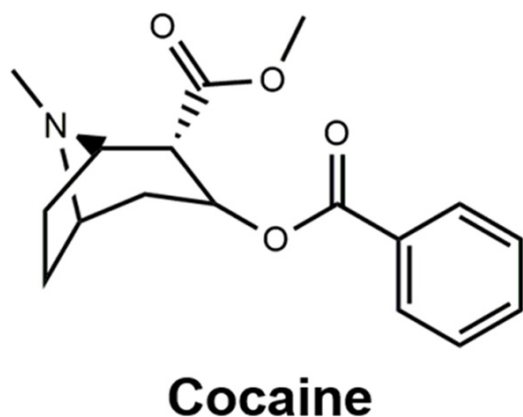


Figure 1. Structure of cocaine.

than a century. In general, the function of the local anesthetic is limited to the site of administration. Despite its long history of use, the working mechanisms underlying the functions of local anesthetics have not been fully elucidated [9]. Currently, there exist three different theories to reveal possible mechanisms [10]. The first theory is called the *Receptor Site Theory*, which holds that, under physiological conditions, local anesthetics exist in both neutral free base form and cationic form. After local injection, molecules in the form of neutral bases penetrate the interior of nerve cells from the injection site. As the pH inside the cell decreases, the molecular content of the cationic form increases. This then competes with the sodium ion for the sodium channel receptor by reducing the number of activated channels, decreasing the ion flux in the open channel, and suppressing the channel from resting to open and reducing the magnitude and speed of the potential rise. This can block the harmful stimulation signals transmitted by the peripheral nerves to reach the spinal cord or the brain, thereby achieving the purpose of relieving pain. The second theory is called the *Membrane Expansion Theory*, which holds that, the hydrophobic local anesthetic molecules can cause the cell membrane to swell, resulting in a change in membrane structure that narrows the sodium channel, thereby preventing the conduction of action potentials. But the limitation of this theory is that it can only explain the working mechanism of neutral local anesthetics. The third theory is called *Surface Charge Theory*. This theory claims that the lipophilic portion of the local anesthetic forms non-spe-

cific binding with the hydrophobic cell membrane of the nerve fiber, while the positively charged portion of the other side of the molecule (i.e., the protonated amine) accumulates outside the cell membrane. In this way, even if the local anesthetic does not enter the cell, it can still accumulate enough positive charge outside the cell membrane, thereby increasing the transmembrane potential without changing the resting potential of the cell. This could cause depolarization and reduce the probability of reaching the threshold potential, thus producing biological activity. However, one flaw in this theory is that it cannot explain the working mechanism of neutral local anesthetics such as benzocaine.

Local anesthetics prevent noxious stimuli from being uploaded to the central nervous system. They exert a highly targeted effect, without the risk of central facilitation and pain allergy. In addition, due to the location of the local drug administration, the blood concentration is low. Therefore, in the absence of accidental blood entry, there are fewer systemic side effects [11]. These characteristics highlight the advantages of local anesthetics in pain treatment.

In the following sections, we will begin with an introduction to the discovery and development of classic local anesthetics, with a focus on aminoester and aminoamide local anesthetics. Next, we will review the development status of long-acting local anesthetics. Finally, we will introduce some other applications of local anesthetics beyond anesthesia, such as their anticancer, anti-inflammatory, antimicrobial, and antiarrhythmic effects.

The first local anesthetic-cocaine

Cocaine (**Figure 1**) is found in the leaves of several plants, such as *Erythroxylum coca*. Records from archaeological sites in South America show that cocaine has been in use since the 6th century. The Spaniards once banned the use of the coca leaves after conquering the Inca Kingdom in the 16th century, but they later discovered that the daily distribution of quantitative coca leaves could boost the local Indians' energy in mining silver mines. After the coca leaves were imported into Europe, the German scientist Albert Niemann purified it into cocaine in 1860, which marked the beginning of a new era [12].

Phylogeny and the applications of local anesthetics

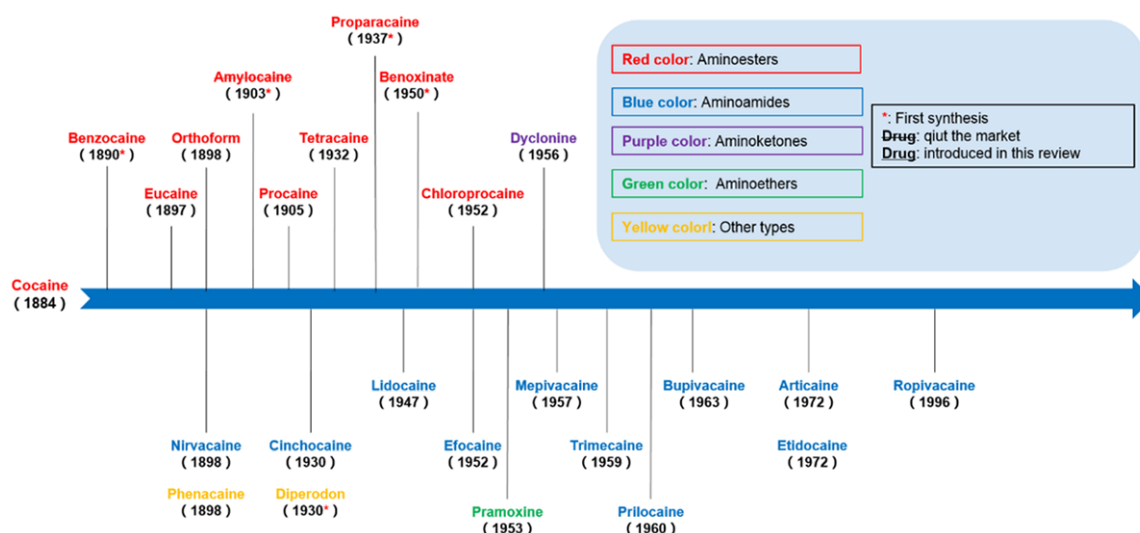


Figure 2. The phylogeny of local anesthetics.

The pharmacologist Karl Damian Ritter von Schroff from Vienna was the first to experiment with cocaine as a narcotic. He found that cocaine has skin insensibility, which he attributed to cocaine acting on the central nervous system. Samuel Percy was the first to propose the use of the coca leaves as an anesthetic in 1856. Sigmund Freud was the first to propose the idea of using cocaine clinically for its local anesthetic properties. After he mentioned this to his colleague and friend Carl Koller, Koller discovered in 1884 that cocaine has analgesic properties in the eye [13].

However, the potential systemic toxicity and the addiction liabilities associated with its use resulted in the abandonment of this agent for most regional anesthesia techniques [12]. Even so, cocaine is an excellent topical anesthetic agent and the only local anesthetic that produces vasoconstriction at clinically useful concentrations. As a result, it is still used to anaesthetize and constrict the nasal mucosa before nasotracheal intubation [14].

The development of classic local anesthetics

Since the discovery of cocaine, a large number of local anesthetics have also been identified and developed. Structurally classified, local anesthetics can be divided into aminoesters, aminoamides, aminoethers, aminoketones, and other structure types. Given the sheer number of local anesthetics, however,

some of the developed local anesthetics were not successfully applied to clinical practice. Therefore, in this review, we only highlight the commonly used local anesthetics, such as aminoesters and aminoamides. The phylogeny of local anesthetics is shown in **Figure 2**. As we all know, the most important clinical properties of local anesthetics are potency, onset, duration of action, and the relative blockade of sensory and motor fibers, etc. In addition to these properties, we also need to consider the neurotoxicity, cardiotoxicity and other adverse reactions of local anesthetics as well as other new effects besides local anesthesia simultaneously.

Important structure type-aminoester local anesthetics

Not long after Niemann discovered cocaine from coca bush in 1860, Koller identified its local anesthetic effect and applied it for the first time to clinical practice in 1884 [13]. However, the side effects of cocaine soon surfaced, such as tissue stimulation and instability to aqueous solution, which prompted chemists to optimize the structure of cocaine. In 1890, Ritsest synthesized ethyl p-amino-benzoate (Benzocaine) [15], an agent that was later found to have a local anesthetic effect. He then continued to synthesize a large number of aromatic acid ester compounds. Thanks to his efforts, both Orthoform and Orthoform New were found, which showed a strong local anesthetic activity. However, the solubility of

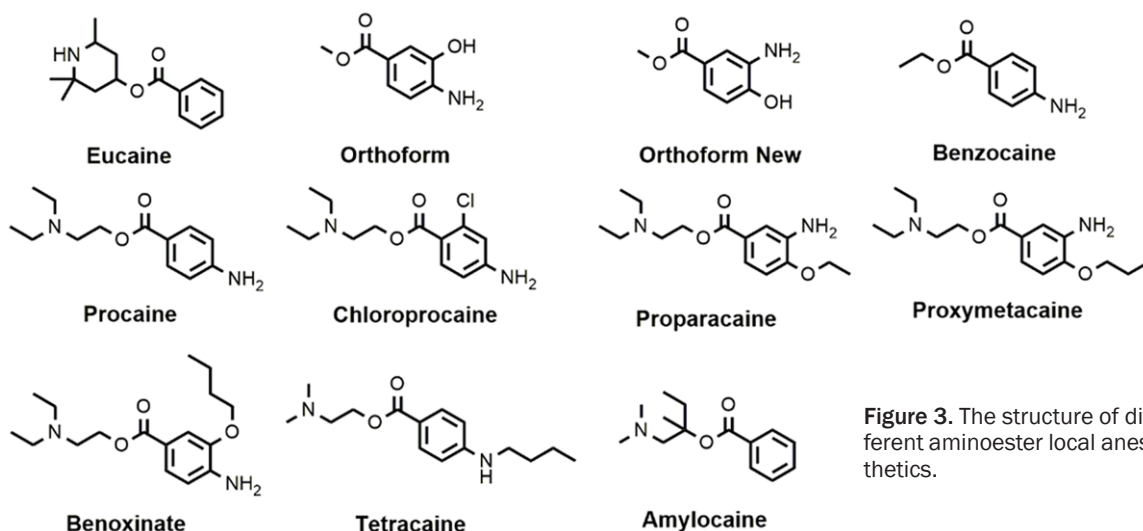


Figure 3. The structure of different aminoester local anesthetics.

Table 1. Physicochemical properties, pharmacological properties, and the applications of different local anesthetics^a

Drug	Physicochemical properties			Pharmacological properties			Applications (Anesthesia)
	MW	pKa (25 °C)	Protein binding (%)	Relative potency	Onset	Duration	
Amylocaine (withdraw)	235	8.9	/	/	/	/	Spinal
Procaine	236	9.0	5.8	1	Slow	Short	Infiltration; Conduction
Chlorprocaine	271	8.7	/	1	Fast	Short	Infiltration; Epidural
Tetracaine	264	8.5	75	6	Fast	Long	Mucosal
Cinchocaine	343	8.8	/	12	Slow	Long	Epidural
Lidocaine	234	7.7	64	2	Fast	Moderate	/
Mepivacaine	246	7.6	78	2	Fast	Moderate	Infiltration; Epidural
Trimecaine	248	7.9	/	3	Fast	Moderate	Infiltration; Epidural
Prilocaine	220	7.7	55	2	Fast	Moderate	Infiltration; Epidural
Bupivacaine	288	8.1	95	8	Moderate	Long	Epidural; Subarachnoid
Etidocaine	276	7.7	94	8	Fast	Long	Epidural; Infiltration
Articaine	284	7.8	94	3	Fast	Long	Oral cavity
Ropivacaine	274	8.1	94	8	Fast	Long	Infiltration

^aThe data in **Table 1** was partially based on an earlier work [85] and reproduced with procaine as the standard in relative potency, onset and duration section.

the drug in the blood is too small to be injected, and its hydrochloride salt is too acidic to be applied. Finally, in 1904, procaine with excellent local anesthetic activity was synthesized [15]. From the structural study of cocaine to the discovery of benzocaine, the optimization of procaine is a prime example of how scientific endeavors are pursued to design and discover new drugs based on the structure of natural compounds.

Next, we will first introduce the important structure type-aminoester local anesthetics. **Figure**

3 reveals the structures of different aminoester local anesthetics. **Table 1** shows the physicochemical properties, pharmacological properties and applications of different local anesthetics, including aminoester local anesthetics.

Amylocaine (also called storvain): Despite the introduction of using cocaine injections for regional anesthesia in 1884, non-addictive substitutes were sought immediately. In 1903, the world's first synthetic and non-addictive local anesthetic-amylocaine, was synthesized

and patented under the name Forneaucaine by Ernest Fourneau at the Pasteur Institute. In other anglophone countries it was referred to as Stovaine, retaining the meaning of the French word “fourneau” (“stove” in English) (The Wood Library-Museum: Stovaine Profile, <https://www.woodlibrarymuseum.org/museum/item/504/stovaine>).

Although amylocaine could be administered topically or injected, it was most widely used for spinal anesthesia. Even though it carried fewer severe side effects than cocaine, the development and clinical use of newer, more effective and even safer local anesthetics like lidocaine, bupivacaine and prilocaine soon followed in the 1940s. In the 1950s, the use of amylocaine was already obsolete [16].

Procaine (also called novocaine): Due to the limited clinical applications of cocaine, it remained in popular use until safer drugs appeared. Niemann hydrolyzed cocaine to benzoic acid in his previous work, and the search for other benzoates precipitated the birth of new local anesthetics. In 1903, researchers synthesized storvain, which was widely used in subarachnoid block before its stimulating effect was discovered. Importantly, the development of procaine by Alfred Einhorn in 1904 was a major advancement. Given that procaine has low toxicity, no drug addiction, and relatively stable properties, it can be widely used not only for local anesthesia, but also for new anesthesia that requires larger doses of drugs. However, as procaine is hydrolyzed by heat, it also has a short duration of action and can cause allergic reactions, which disqualifies it from becoming an ideal local anesthetic.

Chloroprocaine (also called nesacaine): Chloroprocaine was derived from procaine with a chlorine substitution. This chemical modification accelerates the onset of anesthesia, and is twice as potent as procaine, and five times faster than procaine in its metabolic rate. The side effects are only 0.5 times that of procaine. It is characterized by a rapid onset, a short duration of action and low systemic toxicity. The duration of action of chloroprocaine is approximately 30-60 mins. Although the potency of this agent is relatively low, it may be used in a concentration of 3% considering its systemic safety. It is primarily used for extradural analgesia [18] and in anesthesia in obstetrics

because of its rapid onset and low systemic toxicity in mother and fetus. Chloroprocaine has also proven of value for peripheral nerve blocks and extradural anesthesia when the duration of surgery is not expected to exceed 30-60 mins. In order to provide a rapid onset and prolonged duration of anesthesia, it needs to be mixed with other agents such as bupivacaine or amethocaine. But such mixtures with bupivacaine may not result in a long duration of anesthesia.

Chloroprocaine was first used in the United States in 1952. However, after 1980, the use of chloroprocaine declined rapidly in clinical practice, mostly because of reports of prolonged sensory and motor deficits following the accidental subarachnoid injection of this agent [20]. When administered with a dosage of 3% chloroprocaine, it can appear short-lived and cause severe back pain.

Tetracaine (also called amethocaine): Although researchers have tested many other local anesthetics, in the first 50 years following Koller's synthesis of cocaine, only tetracaine and cinchocaine were obtained. Developed in 1930, tetracaine has a relatively strong local anesthetic effect compared with procaine. But the toxicity of tetracaine is also significantly greater than procaine. This agent is used for spinal anesthesia, with a duration of action of 1.5 to 2.5 hrs. It provides a relatively rapid onset of spinal anesthesia (about 3~5 mins), shows excellent qualities of sensory anesthesia and a profound block of motor function. Tetracaine is also an effective topical airway anesthetic. However, the absorption of tetracaine from the tracheobronchial area is extremely rapid. The use of an endotracheal aerosol of tetracaine may even cause death [21]. Tetracaine is rarely used for other forms of regional anesthesia because of its extremely slow onset of action and the potential for systemic toxic reactions when the larger doses required for other types of regional blockade are used. Therefore, for safety concerns, tetracaine is usually not used for infiltration anesthesia.

Another important structure type-aminoamide local anesthetics

Another major development occurred in the 1930s. Erdtman, an organic chemist working in

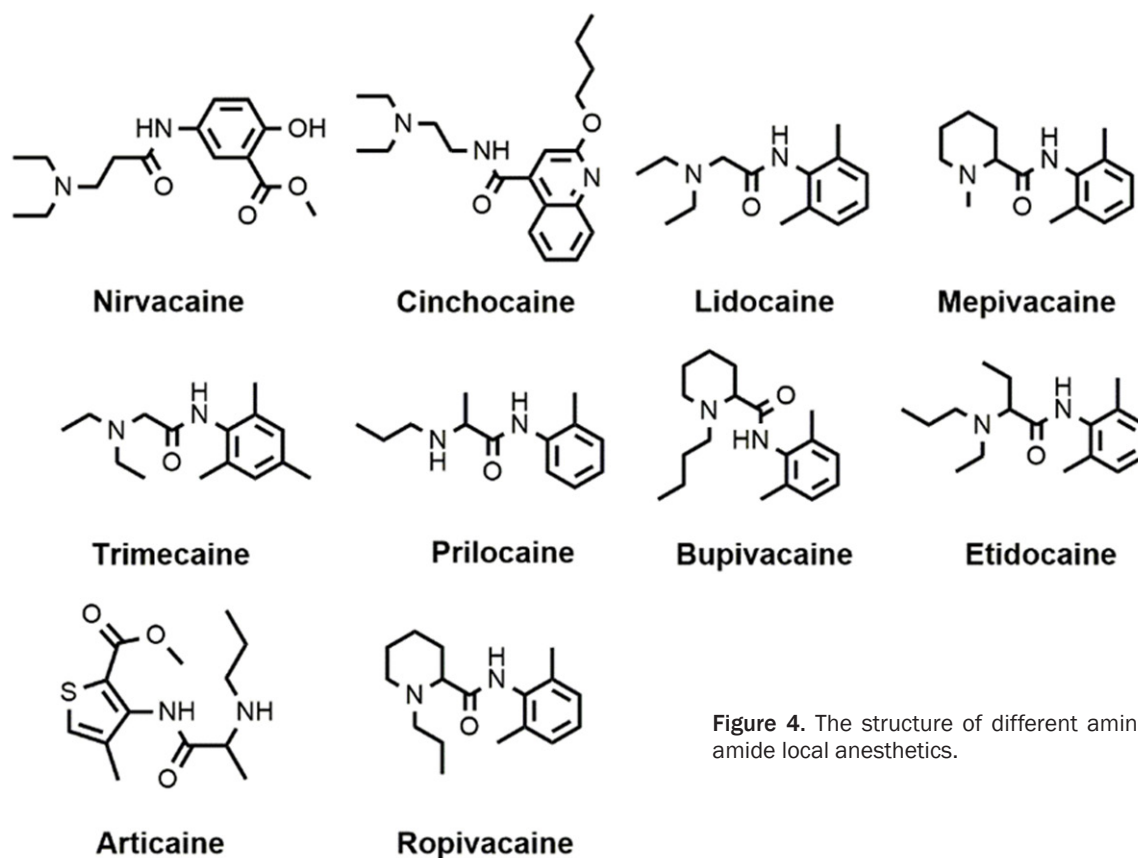


Figure 4. The structure of different aminoamide local anesthetics.

Stockholm, believed in the importance of feeling in chemical analysis. When studying the structure of gramine, he tasted one of precursor substances of gramine. The subsequent numbness he felt immediately became a hot topic that drew the attention of academia and beyond. Edrtman began looking for a derivative for clinical use. Nils Löfgren continued his research and synthesized lidocaine in 1943 [22]. Almost as important as synthetic lidocaine is his systematic study of a range of compounds, which laid the foundation for subsequent local anesthetics research. Through these studies, the researchers synthesized a number of lidocaine derivatives such as mepivacaine, prilocaine, bupivacaine, eticacaine and ropivacaine.

Although the application of these drugs greatly expanded the applications of local anesthetics, they were basically improvements to the same research topic. Due to the emergence of lidocaine, research in the field of membrane physiology witnessed the greatest progress. Two pioneering figures in this field are Hodgkin and

Huxley, whose innovative application of devices such as voltage clamps enables us to understand the mechanisms of nerve conduction and drug blockade at the molecular level [23].

The local anesthetic pharmacokinetic studies conducted during the same period proved to have more practical implications, as they not only advanced people's understanding, but also offered prescriptions for the best drugs and dosages for various local anesthesia methods. Therefore, significant contributions have been made to the establishment of clinical local anesthesia based on a correct, scientific principle.

Figure 4 reveals the structures of different aminoamide local anesthetics. **Table 1** shows the physicochemical properties, pharmacological properties and applications of different local anesthetics, including aminoamide local anesthetics.

Cinchocaine (also called dibucaine): In 1931, cinchocaine was introduced as a local anesthetic. As a local anesthetic of the amide type,

cinchocaine is now generally used for surface anesthesia as Na⁺ channel blocker. It is one of the most potent and toxic of the long-acting local anesthetics, and its parenteral use is restricted to spinal anesthesia [24]. Although the chemical structure of cinchocaine is present in amide, it is still hydrolyzed like other plasma local anesthetics. It can be used clinically to identify the effect of the esterase. The local anesthesia effect of cinchocaine is 22 to 25 times larger than that of procaine, and it lasts for a long time, but the toxicity is 15-20 times greater than that of procaine. Once poisoning occurs, it takes 4-8 hours to reverse the process. It is far more stable than procaine in tissues, so the duration of anesthesia lasts longer (about 3 times longer than procaine). As a highly toxic agent, cinchocaine can cause nausea, sweating, breathing difficulty, sputum, or slang. When used in large doses, it may cause convulsions and facial or skin flushing. Individual cases have allergic reactions. In recent years, new methods have been developed to reduce toxicity produced by cinchocaine. Raquel de M. Barbosa *et al.* used solid lipid nanoparticles (SLNs) as carriers for cinchocaine delivery, which prolonged cinchocaine release and reduced its toxicity. By enhancing its bioavailability, the applications of cinchocaine may be greatly expanded.

Lidocaine (also called lignocaine): As a classic local anesthetic, lidocaine was discovered during systematic investigations at the Institute of Chemistry at Stockholm University (Stockholms Högskola), Stockholm. It was prepared in early 1943 and originally named LL30 by Nils Löfgren (1913-1967) [22]. After lidocaine was used in clinical trials in 1948, it became widely employed because of its potency, rapid onset, and effectiveness. Lidocaine is mainly used for infiltration anesthesia, epidural anesthesia, surface anesthesia (including mucosal anesthesia for thoracoscopic or abdominal surgery) and nerve block. It can also be used for ventricular premature beats and ventricular tachycardia after acute myocardial infarction, as well as digitalis poisoning, cardiac surgery, and ventricular arrhythmias caused by cardiac catheterization, which are usually ineffective for supraventricular arrhythmias. Lidocaine carbonate is used for low epidural anesthesia and brachial plexus block anesthesia. Although lidocaine has a wide range of local anesthetic

effects, it may also induce some adverse effects on the central nervous system, causing such reactions as lethargy, paresthesia, muscle tremor, convulsions and coma. It also can cause hypotension and bradycardia. Excessive blood levels of lidocaine can cause atrial conduction velocity to slow down, induce an atrio-ventricular block, and inhibit myocardial contractility and cardiac output [27].

Mepivacaine (also called cabocaine): Mepivacaine is an amide local anesthetic. In 1957, mepivacaine was applied to clinic practice [28]. Its chemical structure is similar to that of lidocaine, on which the amine is part of a piperidine ring [29]. Compared with lidocaine, mepivacaine has a fast onset speed, a moderate duration of action and a strong anesthetic effect. In addition, it is stable and carries less toxicity and fewer side effects. When it reaches a certain concentration, the penetration ability of cations such as sodium ions and potassium ions on the nerve cell membrane can be reduced, thereby preventing the conduction of nerve impulses. It is a new local anesthetic used in the clinical department of stomatology in recent years, mainly used for squat treatment and endodontic treatment. When concentrations vary from 0.5 to 2.0%, it may be used for extradural, infiltration and peripheral nerve blocks.

There are some other differences between mepivacaine and lidocaine. For example, mepivacaine as a topical anesthetic agent is not as effective as lidocaine. In addition, mepivacaine is not usually applied for obstetric anesthesia because the metabolism of mepivacaine is markedly prolonged in the newborn fetus. However, the toxicity of mepivacaine seems less severe than lidocaine in adults [30], and the vasodilator activity of mepivacaine is less strong than that of lidocaine. In addition, the use of adrenaline affects the duration of anesthesia of mepivacaine because mepivacaine has weaker vasodilating activity than lidocaine.

Trimecaine (also called mesocaine): Trimecaine is an amide-type local anesthetic with a stronger anesthetic effect than procaine and lidocaine. It was prepared in 1948 by Nils Löfgren *et al.* (patent number: US 2441498). Infiltration anesthesia and conduction anesthesia appear after 1 to 1.5 minutes. The action time of trime-

caine is longer and can be maintained for about 3 hours, while the analgesic effect around the wound can be maintained for up to 8-12 hours. Trimecaine can be used for infiltration anesthesia, conduction anesthesia and epidural anesthesia [31]. The toxicity of trimecaine is less severe than that of procaine, lidocaine, and tetracaine.

Prilocaine: Prilocaine was prepared in 1960 by Nils Löfgren *et al.* [32]. Prilocaine belongs to the amide family of local anesthetics and has a similar effect to lidocaine. It has a relatively rapid onset of action, a moderate duration of anesthesia and a profound depth of conduction blockade. Compared with lidocaine, it shows a significantly weaker vasodilating effect, less toxicity and less accumulation. As prilocaine has a significantly weaker vasodilating effect, it is particularly useful in patients with contraindicated adrenaline. A significant portion of prilocaine is metabolized or sequestered in the lungs and is rapidly metabolized by the liver in the body, with less toxicity than lidocaine. Prilocaine is indicated for epidural anesthesia, block anesthesia and infiltration anesthesia. Currently, it is not commonly used in clinical practice and is mainly used for local infiltration anesthesia or intravenous anesthesia, a 1% solution for infiltration anesthesia; a 2% or 3% solution for various nerve block or epidural anesthesia. When the dose of prilocaine exceeds 600 mg, o-toluidine produced by metabolism, hemoglobin was reduced to methemoglobin [33]. And when blood methemoglobin exceeds 1.5 g/dl, complications such as cyanosis and hemoglobinuria may occur. Thus, it can cause an eliminated use in obstetrics. Once this symptom occurs, 1 mg/kg of methylene blue can effectively treat methemoglobinemia. For patients receiving other medications (such as sulfa drugs) that may cause methemoglobinemia, prilocaine stands out as one that can aggravate the formation of methemoglobin.

Bupivacaine: In 1957, bupivacaine was synthesized together with mepivacaine by B. Ekenstam *et al.* [29]. It contains a cyclic amino group in its structure and the aliphatic chain is composed of butyl group instead of a methyl one. As the first single compound long-acting amino amide local anesthetic, bupivacaine may have had the greatest influence on regional

anesthesia since lidocaine appeared. In 1973, it was introduced to the USA. Bupivacaine has an acceptable onset, a long duration of action, a profound conduction blockade, and a significant separation of sensory anesthesia and motor blockade. It can be used for infiltration, peripheral nerve block, epidural, and spinal anesthesia with concentrations of 0.125%, 0.25%, 0.5%, and 0.75%, respectively. But it cannot be used for topical anesthesia. When it was applied for surgical anesthesia, the average duration of bupivacaine varies from 3 to 10 h. In some special situations, when this drug is used for major peripheral nerve blocks such as brachial plexus blockade, the duration of effective surgical anesthesia may last up to 24 h, with complete recovery of sensation afterwards. Another important application of bupivacaine appears in the area of obstetric analgesia for labor. During labor, it can achieve adequate analgesia without significant motor blockade, so that the patient is able to move her legs. In addition, bupivacaine is also widely used for spinal anesthesia [34]. Compared with amethocaine, it shows little difference in terms of onset, spread, and duration of spinal blockade. However, the frequency of satisfactory anesthesia may be greater with bupivacaine than with amethocaine. In the 1980s, there were some studies showing that bupivacaine may have severe cardiotoxicity after it was administered [35, 36]. From then on, the pharmaceutical industry has set out to find a less toxic, long-acting drug which can distinguish sensory and motor blockade similar to bupivacaine. Bupivacaine consists of racemic mixture, and its S-(-)-form has less toxicity than the R-(+)-form, or with the racemic mixture [37]. The enantiomers of bupivacaine were studied in vivo between 1991 and 1996 [38]. Finally, they chose the S-(-)-enantiomer of bupivacaine (Levobupivacaine) for further evaluation in clinical practice [39].

Etidocaine: Etidocaine was prepared in 1972 by H. J. F. Adams *et al.* (patent number: DE 2162744). It is characterized by a very rapid onset, a prolonged duration of action and profound sensory and motor blockade. Etidocaine may be used for peripheral nerve blockade, infiltration and extradural anesthesia [40]. Compared with bupivacaine, it has a more rapid onset of action. When enough sensory anesthesia is required, etidocaine produces a more

profound motor blockade. As a result of this property, it is mainly used for surgical procedures involving neuromuscular blockade. Since etidocaine could not distinguish the blockade of sensory and motor fibers, its use was limited to obstetric extradural analgesia and postoperative pain relief.

Articaine: Articaine is a local anesthetic developed by Hoechst AG (Germany) in 1972. It is mainly used for oral local anesthesia [41]. The pain of the local submucosal anesthesia injection is significantly weaker than that of lidocaine. The local anesthesia of articaine has a fast onset time (about 4 minutes) and a long duration (about 2.4 hours). It has strong invasiveness and local penetration ability to the tissue. It is safe and effective during infiltration. It is especially suitable for common alveolar surgical treatment. Compared with lidocaine's block anesthesia, it uses local submucosal infiltration anesthesia to avoid complications such as deep hematoma infection and nerve damage caused by conduction anesthesia. At the same time, articaine uses international card syringes and matching needles, which are easy to use and are especially suitable for oral high-pressure injection because they can avoid liquid leakage. The disposable needle used in combination is designed with a small diameter in order to lessen pain at the injection point. If used in combination with a topical anesthetic cream, it can basically achieve painless tooth extraction. Articaine belongs to a new generation of local anesthetics. It may have neurotoxicity and cause adverse reactions that vary from one individual to another.

Ropivacaine: Ropivacaine is a new type of pure (S)-(-)-enantiomer long-acting amide local anesthetic developed by Astra Pharmaceuticals (Sweden). It was initially tested in 1990 and later introduced to clinical practice in 1996. Ropivacaine has the dual effects of analgesia and anesthesia. It is widely used for nerve block anesthesia, local infiltration anesthesia and epidural anesthesia. Its distinguishing pharmacological characteristic is low cardiotoxicity [43]. When administered at equivalent doses, ropivacaine is less cardiotoxic than bupivacaine, but more cardiotoxic than lidocaine. And the separation of sensory block and motor block is obvious, with peripheral vasoconstriction. Therefore, the drug is especially

suitable for postoperative analgesia and obstetric anesthesia. Studies have shown that different modes of administration of ropivacaine have different pharmacokinetics and that the peak plasma concentration is closely related to dosage. In different species, the absorption can be single-phase or biphasic. Both ropivacaine and bupivacaine may have similar central toxicity, and the dose of convulsions is nearly equal [44].

Developing better local anesthetics (long-acting local anesthetics)

The local anesthetics currently used in clinical practice have a limited duration of action, with the analgesic time for a single administration falling short of 8 hours on average [45]. While they can satisfy the needs of most surgical or invasive operations, they are far from ideal in the treatment of postoperative pain, chronic pain, etc. Therefore, prolonging the action time of local anesthetics and developing long-acting local anesthetics that meet clinical needs have an important clinical significance and broad market prospects.

The methods for developing long-acting local anesthetics mainly include the addition of synergists to traditional local anesthetics, the continuous pumping of drugs around the nerves, the use of material carriers with controlled release functions, other types of sodium channel blockers, and the development of new compounds.

Adding synergists to traditional local anesthetics

α adrenergic receptor agonist: The addition of α adrenergic receptor agonists, such as low concentrations of adrenaline, norepinephrine or ephedrine to local anesthetics can prolong the duration of action [46]. After local injection of the anesthetic, some of the drug molecules diffuse into the blood vessels and cannot act on the peripheral nerves to produce anesthesia. In addition to cocaine, most local anesthetics can dilate blood vessels, thereby increasing the amount of drug entering the blood vessels. The drug residuals left in the vicinity of the nerve are reduced. α adrenergic receptor agonists enhance the anesthetic effect by contracting blood vessels, reducing the number of local anesthetic drugs entering

the blood circulation and increasing the number of drugs at the site of action. Since the systemic side effects of local anesthetics are related to the plasma concentration level, reducing vascular absorption can slow down the rate and extent of blood drug concentration and reduce systemic side effects. However, vasoconstrictor drugs extend the duration of local anesthesia to a limited extent and do not fundamentally achieve long-acting anesthesia.

Dexmedetomidine is a selective α_2 adrenoceptor agonist. Brummett *et al.* reported that dexmedetomidine could prolong the duration of action of bupivacaine or ropivacaine. Clonidine is another selective α_2 adrenergic receptor agonist. Nasir *et al.* found that clonidine significantly prolonged the duration of ropivacaine effects for the postoperative analgesia in patients who underwent upper arm surgeries.

Opioids: Opioids such as morphine, fentanyl, and buprenorphine can enhance the analgesic effect and reduce the amount of local anesthetics [50-52]. However, opioids are less effective in prolonging the duration of action of local anesthetics. Due to the reduced amount (concentration) of local anesthetics, epidural anesthesia may occur only to block sensory function while retaining motor function. This sensory-sport separation anesthesia is widely used in childbirth and postoperative analgesia.

Magnesium agent: Magnesium sulfate is an N-Methyl-D-aspartic receptor (NMDA receptor) antagonist that has been used for intrathecal analgesia since the 20th century. Whether or not magnesium sulfate is a potentiator for local anesthetics remains controversial. Pre-rana N. Shah *et al.* [53] found that intravenous magnesium sulfate, when given as a bolus, followed by an infusion, delayed and decreased the need of rescue analgesics after spinal anesthesia. Eizaga Rebollar *et al.* [54] argued that with its high safety and low cost, magnesium sulfate has a multitude of potential applications in pediatric anesthesia and could be considered a super adjuvant.

Glucocorticoid: Peripheral nerve block (infiltration of local anesthetic around a nerve) is used for anesthesia or analgesia. A limitation to its use for postoperative analgesia is that the analgesic effect lasts only a few hours, after which moderate to severe pain at the surgical site may call for the need for alternative analgesic

therapy. Several adjuvants have been used to prolong the analgesic duration of peripheral nerve block, including perineural or intravenous dexamethasone. Pehora *et al.* found that when used as an adjuvant to peripheral nerve block in upper limb surgery, both perineural and intravenous dexamethasone may prolong the duration of sensory block and are effective in reducing postoperative pain intensity and opioid consumption.

Other commonly used synergists: Neostigmine has the effect of enhancing local anesthesia, but its side effects, such as nausea and vomiting, limit its clinical applications. Results from Kumari Vasantha *et al.* indicated that intrathecal neostigmine is associated with significantly prolonged sensory, motor blockade, and effective postoperative analgesia of bupivacaine. Midazolam combined with ropivacaine for fistula anesthesia also achieved long-term postoperative analgesia [57]. Sodium bicarbonate shortens the onset time of local anesthetics by increasing the amount of nonionic drug molecules in the drug solution. However, currently, these synergists are not widely used in clinical practice, possibly because of their systemic side effects and local tissue irritation.

Continuous pumping of drugs around the nerve

The embedded catheter is placed around the peripheral nerve and a local anesthetic is continuously administered through the catheter to produce a long-term anesthetic effect. The method is widely used in the fields of labor analgesia, postoperative analgesia and the like. However, the technical requirements for embedding the catheter are high, and postoperative changes in the position of the patient may cause catheter displacement, nerve injury, bleeding, etc. [58]. In the case of special epidural catheter anesthesia, if the catheter accidentally penetrates the dura mater, it may cause an excessive concentration of the local anesthetic to enter the subarachnoid space, resulting in serious consequences such as spinal cord injury and total spinal anesthesia. Improper use may even lead to certain disabilities or even death.

Since sensory nerves and motor nerves are simultaneously encapsulated in the nerve sheath, local anesthetics may block sensory and motor function at the same time in periph-

eral nerve block and epidural anesthesia, causing sensory loss and muscle paralysis. Long-term muscle paralysis is not conducive to early postoperative activities or functional exercise, which is one of the drawbacks of the embedded catheter method.

Use a material carrier with controlled release

Drug delivery systems are widely used in pharmaceuticals and biological agents. The use of materials with sustained or controlled release characteristics (including liposomes, nanomaterials, microspheres, microneedle arrays, etc.) to load local anesthetics is a hot topic in this field [59]. The main preparation method of the drug carrier or the sustained-release system is to encapsulate or load the drug into a special material and to achieve long-acting effects by slowly releasing the drug in the body.

The relatively short duration of effect of local anesthetics has been addressed by encapsulation in drug delivery systems. Co-delivery with a single compound that produces an adjuvant effect on nerve block but without intrinsic local anesthetic properties can further prolong the nerve block effect. Rwei *et al.* found that the co-delivery of liposomal-dexamethasone phosphate and liposomal-dexmedetomidine enhanced the efficacy of liposomal-bupivacaine. This benefit was also seen with the co-delivery of both adjuvant molecules in the unencapsulated state, but with marked systemic toxicity.

Exparel® (Bupivacaine Liposome Injectable Suspension, Pacira Pharmaceuticals Inc., San Diego, CA) is a novel formulation of bupivacaine available in the United States since mid-2012. Bupivacaine is encapsulated within multivesicular liposomes and released slowly, which is claimed to prolong its duration up to 72 hours. Its primary use is surgical wound infiltration. However, due to the inherent physical and chemical characteristics of liposomes, the encapsulation efficiency and the total amount of drug-loaded bupivacaine are limited, thus restraining the intensity of action in the large peripheral nerve trunk block [61].

Other types of sodium channel blockers

The site where the traditional local anesthetics blockade the sodium channel is the intracellular cytoplasmic side. A type I sodium channel

blocker is represented by tetrodotoxin, which is located on the cell surface side of the sodium channel. Due to the different sites of action, such sodium channel blockers do not need to penetrate the cell membrane and therefore have high blocking efficiency. However, the clinical application of this class of drugs is limited due to its toxicity. Local absorption into the blood can cause respiratory muscle paralysis, leading to serious adverse reactions [62].

Neurotoxicity has been reported with tricyclic antidepressants (TCAs) used as local anesthetics. Barnett *et al.* investigated whether TCAs can cause tissue injury, particularly myotoxicity, as is the case with many local anesthetics. Their results indicated that TCAs do not appear to offer any advantages over conventional local anesthetics (such as bupivacaine) and may even have increased toxicity.

Developing new compounds

QX-314: It is difficult for Lidocaine's quaternary ammonium salt derivative QX-314, originally a research tool, to actively permeate fat-soluble cell membranes, because it is permanently positively charged. However, it can effectively block sodium ion current after injection into cells. In 2007, Binshtok *et al.* showed that QX-314 can be administered into the nerve cells via the activated transient receptor channel vanilloid 1 (TRPV1) via rat sciatic nerve. QX-314 can also enter cells through the transient receptor channel subtype A1 (TRPA1), the adenosine triphosphate receptor (P2X3), and the transient receptor channel subtype M8 (TRPM8). However, due to the strong irritancy of TRPV1 agonist capsaicin, the combination of capsaicin and QX-314 has been clinically limited [65]. Despite this, the long-acting and selective blocking based on TRPV channels and QX-314 have become a research hotspot. Brenneis *et al.* used a combination of clinically used local anesthetics and other sodium channel agonists with QX-314. They found out that bupivacaine is the most potent agonist of transient receptor channel (TRP), which not only stimulates TRPV1, but also stimulates TRPA1 and non-TRP channels, thereby promoting the entry of QX-314 into nerve cells and resulting in long-term local anesthetic effects.

It has been reported that local anesthetics such as lidocaine and bupivacaine when com-

bined with QX-314 can produce long-term nerve block in rats, showing certain clinical prospects [66, 67]. It is well known that the combination of local anesthetics may result in increased local neurotoxicity and systemic toxicity. In the above studies, lidocaine and bupivacaine are used at higher concentrations. Although the evidence obtained in animal experiments has been compelling, more studies are still necessary to address safety and pharmacodynamic concerns before they can be used in clinical settings.

Tetrodotoxin (TTX) combined with QX-314 can produce up to 15 hours of blockade in rat sciatic nerve block, 8 to 10 times that of QX-314 alone, but with a mild to moderate muscular inflammatory response [68]. Therefore, it is difficult to weigh the advantages and disadvantages of the combination of TTX and QX-314. Interestingly, TTX itself has an excellent effect as an analgesic drug in many animal models and even human cancer pain.

EN3427: EN3427 is an analog of QX-314. Banerjee *et al.* found that EN3427 produces effective and long-lasting analgesia in 2 rodent pain models. The analgesic effects of EN3427 are significantly longer-lasting than lidocaine and are further extended when EN3427 is combined with lidocaine. However, a high concentration (1 g/L^{-1}) of EN3427 can cause more serious local tissue toxicity, and the dose-effect relationship between concentration and tissue toxicity is unknown. In addition, lidocaine itself has concentration-dependent tissue irritancy, so EN3427 is safe. There is no complete study of local tissue response or corresponding clinical trials of EN3427.

Neosaxitoxin: Neosaxitoxin (neoSTX®) is a biological neurotoxin, an analog of saxitoxin, which belongs to type I sodium channel blocker. Compared with traditional local anesthetics, its local muscle and neurotoxicity are negligible and its sodium block resistance is greatly increased [70]. Neosaxitoxin when used alone is able to block the sciatic nerve of rats for 0.2 hours. Combined with bupivacaine, it can produce a blocking effect of up to 6 hours. When epinephrine is added, it could last for 48 h. The time to apnea, arrhythmia and cardiac arrest after intravenous injection of neosaxitoxin was significantly longer than bupivacaine. However, after the local administration of neosaxitoxin to

the unilateral sciatic nerve, transient analgesia and limb paralysis also appeared in the contralateral limb, suggesting that the systemic absorption was rapid after local administration, and that the systemic distribution could cause limb paralysis. The dose-climbing test showed that the median lethal dose of neosaxitoxin was $4.9 \mu\text{g/kg}^{-1}$, and the median lethal dose of bupivacaine combined with $5.7 \mu\text{g/kg}^{-1}$, and the dose of drug production ($3 \mu\text{g/Kg}^{-1}$) is close; the main manifestations of death are dyspnea and respiratory arrest. The above test results suggest that although the toxicity of neosaxitoxin is lower than that of tetrodotoxin, it remains a big concern [71].

Other applications beyond anesthesia of local anesthetics

The use of old drugs for new purposes pertains to the use of known drugs to treat diseases such as non-indications. Advances in science in recent years have illuminated the role that traditionally used drugs can play in the treatment of other human diseases beyond their original scope, often showing excellent results and few side effects. Take metformin as an example. Metformin is a classic drug for the treatment of type 2 diabetes. But scientists from the U.K. have found that pancreatic cancer stem cells are actually more prone to aerobic metabolic processes, according to which diabetes treatment such as metformin can be used to inhibit pancreatic cancer stem cell growth [72]. Another example is salicylic acid, which is a key compound in the non-steroidal anti-inflammatory drugs aspirin and diflunisal. Researchers at the Gladstone Institutes found that salicylic acid can block inflammation and cancer. Salicylic acid and diflunisal inhibit the activity of two key proteins that control gene expression in the body, while the two sister proteins, p300 and CREB-binding protein (CBP) are special. Epigenetic regulators control the levels of key proteins that promote inflammation and participate in cell growth; salicylic acid and diflunisal can inhibit the activity of the p300 and CBP proteins and inhibit the effects of cellular damage caused by inflammation [73].

In addition to the anesthetic effect of local anesthetics, they also have some other direct or indirect effects, such as anticancer, anti-

inflammatory, antimicrobial, antiarrhythmic effect, and so on.

Anticancer effect

Procaine is an aminoester local anesthetic. In addition to its local anesthetic effect, its anticancer effect has also been documented by scientists. Chang Li *et al.* investigated its effect on a human colon cancer cell line (HCT116) *in vitro* and revealed the mechanism of its effect. Their results also indicated that procaine (2 μ M) significantly inhibited cell viability, increased the percentage of apoptotic cells, and decreased the expression level of RhoA in HCT116 cells in a dose-dependent manner. It also increased the proportion of HCT116 cells in the G₁ phase, downregulated cyclin D1 and cyclin E expressions, and remarkably inhibited cell migration. But these effects could be reversed by PCA+pc-RhoA. The levels of p-ERK, p-p38MAPK and p-FAK also decreased after treatment with procaine (2 μ M).

Another aminoamide local anesthetic is lidocaine, which may have anticancer effects for certain different types of cancer. D'Agostino *et al.* found that, at clinical concentrations (10 or 100 μ M), lidocaine significantly inhibited CXCR4 signaling and blocked human breast cancer progression and metastasis. Ferreira *et al.* used 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) to complex with lidocaine (HP- β -CD-lido) and evaluated their effect on cell viability and the proliferation of human tongue squamous cell carcinoma SCC9 and SCC25 with MTT assay and SRB assay. Their results indicated that HP- β -CD-lido (4000 μ M) has a stronger inhibitory effect on proliferation and cell viability of SCC9 and SCC25 compared with lidocaine (4000 μ M) or HP- β -CD (4000 μ M) alone, respectively. In another study, *et al.* conducted an investigation into human gastric cancer cells (SGC7901, BGC823) with lidocaine *in vitro*. Their data showed that lidocaine could significantly suppress proliferation, migration and invasion and induce apoptosis in a dose-dependent manner in human gastric cancer cells (SGC7901, BGC823). For the mechanisms of lidocaine in these two different kinds of human gastric cancer cells, their results indicated that the expression of Bcl-2 was decreased, the level of Bax was increased, the protein expression of the MAPK pathway was also changed, and that p-p38 was increased

simultaneously, while the level of p38 was not changed with the treatment of lidocaine.

Ropivacaine is an aminoamide local anesthetic. Zheng Q *et al.* [78] found that ropivacaine (1000 μ M) inhibited proliferation in a dose- and time-dependent manner by arresting cells at the G2/M stage and inducing apoptosis in the CML cell line (K562, LAMA84). It induced apoptosis and inhibited colony formation in CD34 progenitor or stem cells derived from patients with blast phase. When ropivacaine (500 or 1000 μ M) is combined with imatinib (1 μ M) or dasatinib (20 or 200 nM) (Bcr-Abl tyrosine kinase inhibitors), it proves more effective in targeting CML cell lines as well as BP-CML CD34 cells than imatinib or dasatinib alone. The mechanism of ropivacaine acts on CML cells (K562) by inhibiting the PI3K/Akt/mTOR pathway.

Anti-inflammatory effect

In addition to its anticancer effect, lidocaine also has an anti-inflammatory effect. Kuan Ming Chiu *et al.* [79] found that, an *i.p.* injection of kainic acid (KA) (15 mg/kg) could lead to neuronal death in the CA3 pyramidal layers of the hippocampus, but this effect was attenuated by the systemic administration of lidocaine (0.8 or 4 mg/kg, *i.p.*) 30 mins before KA injection. The mechanism revealed that the expression of proinflammatory factors such as IL-1 β , IL-6 and TNF- α was decreased by the lidocaine pretreatment in the hippocampus of rats. In another study, Ryo Tateuchi *et al.* evaluated the changes of the apparent partition coefficient of indomethacin ($\log P'_{IND}$) caused by clinically used local anesthetics (lidocaine, tetracaine, mepivacaine, bupivacaine and dibucaine) and by structurally similar basic drugs (procainamide, imipramine and diltiazem). Their results showed that the local anesthetics and structurally similar drugs could function as phase-transfer catalysts, increasing the membrane permeability of indomethacin (an acidic nonsteroidal anti-inflammatory drug) via heterogeneous intermolecular association. This method may improve efficiency and decrease the side effects of indomethacin when used on patients.

Antimicrobial effect

Antimicrobial agents represent another important kind of commonly used drugs. Thanawat

Kaewjiaranai *et al.* [81] reviewed local anesthetics as antimicrobial agents used in dentistry from 1970 to 2018, covering many kinds of different local anesthetics such as lidocaine, procaine, bupivacaine, and mepivacaine, among others. These local anesthetics function against different oral microorganisms alone or in combination with other drugs. Although local anesthetics can be considered as an adjunct to the use of traditional antibacterial drugs in clinical or laboratory settings, minimal information is available on the antimicrobial efficacy of anesthetic agents in dental clinical settings. The final use of local anesthetics in clinical practice requires more studies. In another study, Bibi Marjan Razavi *et al.* reviewed the antimicrobial action of local anesthetics. They collected data from different databases such as PubMed, Scopus, and Web of Science using such keywords as “antimicrobial”, “antibacterial”, “antifungal”, “bactericidal”, “fungicidal”, “local anesthetic”, “lidocaine (lignocaine)”, “bupivacaine”, “prilocaine”, “mepivacaine”, “ropivacaine”, “articaine”, “procaine”, “tetracaine (amethocaine)”, “dibucaine (cinchocaine)”, and “benzocaine” without setting a limit on publication time. They found that the most studied bacteria are *E. coli*, *P. aeruginosa*, and *S. aureus*. Moreover, among different local anesthetics, lidocaine is the most studied preparation. The mechanisms underlying local anesthetics’ antimicrobial activity include the disruption of the bacterial cell membrane, the inhibition of cell wall synthesis, the dysfunction of cellular respiration, an alteration in DNA synthesis, the lysis of protoplasts, an alteration in permeability and leakage of intracellular components, ultrastructural changes, etc. Further research is needed in this area to elucidate these mechanisms.

Antiarrhythmic effect

Lidocaine is a local anesthetic commonly used in medical clinics. In 1963, it was originally used to treat arrhythmia. As a ventricular premature beat of acute myocardial infarction and ventricular tachycardia, it is specially designed for the prevention and treatment of acute myocardial infarction and various heart diseases with rapid ventricular arrhythmia. It is also the preferred drug for overspeed and ventricular tremor [83].

Based on the chemical structure of clinical common local anesthetics, Dmitrii V. Kalinin *et al.* designed, synthesized and evaluated the local anesthetic and antiarrhythmic activities of a series of N-alkylproline anilides *in vivo*. Their results showed that Compound 4o was the most promising compound in terms of surface anesthesia and antiarrhythmic effects, and that the toxicity was significantly lower than the toxicity of the reference drugs. Compound 4p exhibited a relatively low anesthetic activity, but it may be further developed as an antiarrhythmic agent with low toxicity.

Conclusion

Since cocaine was discovered and developed as a local anesthetic, a large number of derivatives have been developed by researchers at pharmaceutical companies and university research institutions. The advent of procaine and lidocaine has marked a new era for the development of local anesthetics. The discovery of local anesthetics such as bupivacaine and ropivacaine in the later stage enriched the clinical applications of local anesthesia. However, the classic local anesthetics still have certain defects. In recent decades, no local anesthetics have been found for truly new chemical entities (NCE). Due to the urgent need for long-acting local anesthetics, the next generation of new local anesthetics is likely to achieve long-term analgesia. And many of the possible breakthroughs in the development of new long-acting local anesthetics may come from drug carriers, derivatives of existing local anesthetics, TRP channel-based sodium blockers QX-314, other class I sodium channel blockers, or existing local anesthetics in combination with hormones, opioid receptors agonist/blockers and HCN receptor agonists. Among them, bupivacaine liposomes and analogs of saxitoxin are undergoing clinical trials and are expected to be applied on a large scale to clinical practice. However, the bottleneck in the development of long-acting local anesthetics is the conflict between the duration of drug action and/or the intensity of effect and drug toxicity. In general, the longer the action time, the higher the intensity of action and the greater the systemic toxicity and tissue toxicity. The repair ability of nerve tissue damage is very limited, and once it is damaged, the consequences are more serious. Therefore, safety has always

been a major concern restricting the development of new long-acting anesthetics. When safety is guaranteed, ensuring sufficient analgesia intensity is another important goal for the development of new local anesthetics. Because of the tissue and systemic toxicity of existing amide and ester local anesthetics in a concentration-dependent manner, new long-acting local anesthetics with novel molecular structures may become a new direction in the field.

Research into the new role of local anesthetics represents an important direction in academia, especially its anticancer, anti-inflammatory, antimicrobial, antiarrhythmic effects. Whether it exerts a direct effect or functions as an adjunct, it holds out much promise for the treatment of diseases in clinical practice. Therefore, more research is needed in the future to further clarify the new effects of such classic drugs.

Disclosure of conflict of interest

None.

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