LAs in Pain, Inflammation, and Other Clinical Conditions

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The use of low-dose local anesthetics in low concentrations for therapeutic, non-anesthetic purposes, known as neural therapy, has significantly transformed patient care by providing rapid, effective, long-lasting and safe relief of pain, inflammation and other clinical conditions while minimizing recovery time.

Keywords: local anesthetics ; pain ; neural therapy ; therapeutic local anesthesia ; procaine ; lidocaine

1. Introduction

The use of local anesthetics (LAs) for therapeutic purposes dates to their discovery when the Austrian ophthalmologist Carl Koller performed the first surgery using the anesthetic properties of cocaine in 1894 [1]. In 1905, Einhorn synthesized the local anesthetic procaine, and, a year later, Spiess reported the rapid reduction of inflammation with procaine injections, attributing this effect to its action on the nervous system [2]. Over the years, the medical community has expanded on the pioneering ideas of the Huneke brothers and others, leading to the widespread use of Las for therapeutic purposes in Europe, often referred to as neural therapy (NT) or therapeutic local anesthesia [3][4][5][6][7][8].

The therapeutic use of LAs in the treatment of pain and various other clinical conditions has been well-documented [9][10][11][12] and accepted, as evidenced by its inclusion in the mandatory basic insurance in some countries, such as Switzerland, Austria, or Colombia. Traditionally used in the surgical setting for short-term analgesia, the therapeutic use of LAs now aims to provide sustained relief of pain and other dysfunctions by targeting the autonomic nervous system (ANS). The ANS plays a central role in the regulation of inflammatory and immune processes, (micro) circulation and thus pain, and other clinical conditions [13][14][15][16][17][18][19][20].

One of the intriguing aspects of this therapy is the use of low-dose, short-acting LAs in areas of injury or inflammation, nerves, ganglia, and others, such as myofascial trigger points. The underlying principle is to modulate the auto-regulatory mechanisms and plastic properties of the nervous system, particularly the ANS [4][5][17][18][21][22][23][24][25]. The role of the ANS in the modern understanding of inflammation and pain is fundamental, as ANS controls reflexive neuroimmunological and inflammatory cascades [13][16][17][26][27][28][29].

2. Properties of LAs and Mechanisms of Action

LAs work by blocking voltage-gated sodium channels, inhibiting nerve conduction and thereby producing local analgesia. Originally developed for surgical applications, newer LAs have been synthesized to prolong the duration of anesthesia. However, therapeutic regulation does not depend on the prolonged action of LAs. Rather, it is the ability to “reset” pathological conduction that matters, regardless of how long this interruption lasts [17][21]. LAs are an important therapeutic option in the analgesic management of pain. Their use in pain relief strategies is logical because they effectively block the conduction of peripheral nociceptive nerve fibers, thereby attenuating the activity of the entire nociceptive system. This includes dampening the response of wide dynamic range (WDR) neurons in the spinal cord and attenuating central sensitization [16][30].

Over time, LAs have been found to exert a range of alternative effects, including modulation of the inflammatory cascade, inhibition of inflammatory mediators, antiarrhythmic [31] protection against thromboembolism [32], antimicrobial activity, and even anticancer properties [33][34][35][36][37][38].

LAs exhibit powerful anti-inflammatory effects acting on both humoral and cellular levels [38], potentially surpassing traditional steroidal or non-steroidal anti-inflammatory agents in efficacy and tolerability [39]. They reduce inflammation while preserving the body’s healing and protective responses, effectively managing pain without delaying healing or

increasing the risk of infection [40]. Furthermore, lower concentrations of LAs can maintain an anti-inflammatory and, consequently, analgesic effect, minimizing the risk of potential toxicity [41].

Beyond the immediate effects of LAs and their alternative properties, it is necessary to consider other mechanisms to account for the sustained therapeutic outcomes observed in conditions like therapy-resistant pain and inflammation. The role of the ANS is important in this context. The previous research postulates the existence of positive feedback loops in pain and inflammatory pathways controlled by the ANS [17][18][25][41]. Interestingly, these basic feedback mechanisms are universal and can be activated by various triggers such as infection, mechanical trauma, or psychological stress [13][17][28][42]. Consequently, the results of this research elucidate why a single agent, such as LAs, can be therapeutically effective in a wide range of clinical diagnoses. In the following sections, the researchers show the importance of the ANS in the emergence of feedback loops and their interruption by LAs.

2.1. Neuronal Reflex Circuitries

The anatomical organization of neuronal pathways, characterized by principles of convergence and divergence, exemplifies a fundamental biological mechanism that facilitates positive feedback loops within reflex circuits [17]. A prime example of this is the convergence of visceral and somatic nociceptive afferents on the same multireceptive neurons in the dorsal horn of the spinal cord (wide dynamic range WDR neurons). Subsequent fibers give rise to divergent efferent pathways that project to: (1) higher brain centers, (2) sympathetic or parasympathetic nuclei within the lateral horn, (3) the anterior horn, innervating the skeletal musculature [5]. Clinically, this can result in increased peripheral myofascial tone and skin turgor, changes in microcirculation, and hyperalgesia, indicating sensitization processes in which the sympathetic nervous system plays a central role. The resulting peripheral sensitization enhances sympathetic hyperactivity, thereby amplifying nociceptive input to the spinal cord [41]. This reciprocal reinforcement between peripheral and central mechanisms constitutes a positive feedback loop involving the ANS [25]. Interventionally, the transient disruption of these reflexive pathways through the administration of LAs may facilitate a reversion to physiological homeostasis [17][20][25]. The strategic application of LAs can be tailored to the individual by targeting specific anatomical structures such as trigger points, scars, sympathetic ganglia, and peripheral nerves. The repeated blockade of sensitized nociceptive afferents by LAs contributes to the modulation of neuroplastic changes within neuronal centers, potentially attenuating “pain memory” [41]. In addition, useful combinations of injections can be applied simultaneously, having a positive effect on inhibitory mechanisms, such as the gate control theory of pain postulated by Melzack and Wall [43], reducing nociceptive transmission at the dorsal horn.

2.2. Pathophysiological Coupling Mechanisms between Sympathetic and Nociceptive Systems

Under pathological conditions, a short-circuit may occur between sympathetic efferent fibers and nociceptive afferents, a phenomenon referred to as “sympathetic afferent coupling” [16][44]. Nociceptive afferents [44][45][46], and even immune cells [47], can express adrenergic receptors. This expression facilitates a pathological nexus where the efferent sympathetic outflow gains the ability to directly activate the afferent nociceptive pathways as well as modulate immune responses, creating a cascade that can potentiate pain and inflammation, thereby establishing a self-perpetuating positive feedback loop [17].

A similar process is called “sympathetic sprouting,” wherein sympathetic fibers undergo morphological changes, elaborating basket-like structures in the dorsal root ganglia of nociceptive afferents under inflammatory and neuropathic conditions [48][49][50]. Such structural reorganization allows for an enhanced and rapid nociceptive response to sympathetic stimuli (peripheral or central), thereby exacerbating pain in a positive feedback loop [5]. LAs have been shown to reduce sympathetic sprouting in dorsal root ganglia with increased spontaneous activity [51][52].

2.3. Sensitization and Neuroplastic Mechanisms

Sensitization processes can induce peripheral and central neuroplastic changes [53], effectively allowing the nervous system to acquire and retain new functional states like learning and memory. This capacity for neuroadaptation extends to the sympathetic ganglia, where it can result in the enhancement of the postsynaptic neuronal response to repetitive presynaptic activity (synaptic long-term potentiation LTP) [54][55][56], showing the efficacy of LAs in indirectly reducing LTP.

Thus, the sympathetic nervous system can engrammatically store “old” stimuli and respond to new physiological stimuli with an overshooting pathological response [17][41][42][54][57][58]. This can be seen as a memory and learning process [28][53][58]. Any activation of the sympathetic system, peripheral or central (including emotions), can amplify symptomatic manifestations, such as pain or inflammation, by establishing positive feedback loops [17][24]. Repeated LA-induced

blockade of sensitized nociceptive afferent neurons also allows modulation of plastic changes in neuronal centers (“pain memory”) [41].

2.4. Neuroimmunological Interactions and Therapeutic Implications

The ANS and the immune system are in a dynamic and intricate communication network, as evidenced by extensive research [13][15][17][19][25][26][27][28][59]. These reflectory neuroimmunological and inflammatory cascades constitute a general reaction principle of the organism under the leadership of the ANS [17]. We could detect several interdependent positive feedback loops that can exacerbate inflammation and pain [17].

Crucially, these feedback loops depend strongly on the ANS, with sympathetic efferents playing an important role alongside the modulatory influence of cytokines and vagal fibers interacting within the sympathetic centers of the brainstem [17]. These loops operate simultaneously, reinforcing each other and perpetuating the physiological response [17].

A remarkable aspect of these neuroimmune interactions is their consistency across disease states, regardless of the nature of the initial stimulus—be it infection, mechanical trauma, or psychological stress [13][16][17][28][42]. This consistency suggests that basic pathological neuroimmune communication can be effectively modulated by LAs, particularly through interventions such as stellate ganglion blocks, which can “reset” these dysregulated pathways [17].

Consequently, the researchers postulated a unified pathogenetic mechanism within the neuroimmune system, predominantly under the regulation of the sympathetic nervous system [17]. This common principle explains the efficacy of stellate ganglion blocks with LA in the treatment of a wide range of conditions such as acute and chronic pain, acute respiratory distress syndrome, pneumonia, traumatic brain injury, post-traumatic stress disorder, autoimmune diseases, heart failure including arrhythmias, microcirculatory disorders, autonomic dysfunction, neurogenic inflammation, complex regional pain syndrome, early systemic inflammatory response in severe trauma, and more [17][19][60][61][62][63][64][65][66][67][68][69].

3. Safety

No significant adverse effects from LAs toxicity were found in the reviewed articles, which is consistent with the established literature that consistently emphasizes the dose-dependent nature of toxicity. The administration of LAs at low doses is remarkably safe. While there have been historical concerns about potential allergic reactions to LAs, particularly procaine, this research and recent research have largely allayed these fears. In this research, lidocaine and procaine emerged as the predominant LAs of choice, with their selection likely influenced by their relatively low toxicity profiles. The prevalence of lidocaine may be attributed to its widespread availability and lower incidence of allergic reactions. However, when evaluated purely from a toxicity standpoint, procaine may be the more prudent choice due to its even lower toxicity, shorter half-life, and lack of reliance on hepatic metabolism, particularly in therapeutic contexts without anesthetic intent.

Any needle-based procedure carries inherent risks associated with puncture, including potential complications such as severe hematoma and pneumothorax. LAs in the cerebrospinal fluid space can compromise vital functions. Importantly, the severity of these complications is dose-related.

This safety, combined with their proven efficacy, underscores the importance of exploring LAs for novel therapeutic applications.

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