Review Article

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Neurotoxicity of local anesthetics in dentistry

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During dental treatment, a dentist usually applies the local anesthesia. Therefore, all dentists should have expertise in local anesthesia and anesthetics. Local anesthetics have a neurotoxic effect at clinically relevant concentrations. Many studies have investigated the mechanism of neurotoxicity of local anesthetics but the precise mechanism of local anesthetic-induced neurotoxicity is still unclear. In addition, it is difficult to demonstrate the direct neurotoxic effect of local anesthetics because perioperative nerve damage is influenced by various factors, such as the anesthetic, the patient, and surgical risk factors. This review summarizes knowledge about the pharmacology of local anesthetics, nerve anatomy, and the incidence, risk factors, and possible cellular mechanisms of local anesthetic-induced neurotoxicity.

Keywords: Dentistry; Local Anesthetics; Neurotoxicity.

INTRODUCTION

In the dental clinic, local anesthesia is an inevitable procedure to carry out various dental treatments. During local infiltration and peripheral nerve blocks, local anesthetics reversibly block the action potentials of neuronal voltage-gated sodium channels and induce analgesia and anesthesia [1]. However, local anesthetics may cause nerve damage and have a toxic effect on various cell types [2,3]. Furthermore, local anesthetic-induced cytotoxicity in many types of cells occurs at clinically relevant concentrations [4-6]. However, the ascertainment of the direct neurotoxic effect of local anesthetics is difficult and complex because perioperative nerve damage can arise from many clinical factors. The incidence of local anesthetic-induced neurotoxicity varies depending on the type of surgery, anesthetic technique, and patient factors [7,8].

In this review, we aimed to summarize knowledge about the pharmacology of local anesthetics and the incidence, risk factors, and mechanisms of neurotoxicity caused by local anesthetics.

PHARMACOLOGY OF LOCAL ANESTHETICS IN DENTISTRY

Structurally, local anesthetics consist of a lipophilic aromatic group, a hydrophilic group, and an amide or ester linkage chain; local anesthetics are divided into amino-amide or amino-ester type [9]. The amide class of local anesthetics in dental cartridges includes lidocaine, articaine, bupivacaine, mepivacaine, and prilocaine. The

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ester class includes benzocaine.

The onset and duration of local anesthetic action are affected by various factors. Local anesthetics are deposited extracellularly in a state of equilibrium between the unionized and ionized form after injection, which is affected by the pH of the surrounding tissue and pKa of the drug. The unionized form crosses the lipid bilayer of the neuronal membrane and blocks voltage-gated sodium channels. There are no significant differences in the pKa among the amide class of local anesthetics, except for bupivacaine, which has a slightly higher pKa, leading to a slow onset of action. High lipid solubility promotes the onset of local anesthesia to a certain degree [10-12]. Local anesthetics with higher degrees of protein binding have a longer duration of action. Bupivacaine provides a long duration of anesthesia in soft tissue in the arches and pulp of mandibular teeth [13].

NERVE ANATOMY

To discuss the neurotoxicity of local anesthetics, it is necessary to become well-acquainted with the anatomy of a nerve. Nerve fibers are surrounded by the endoneurium, which is a layer of loose connective tissue and Schwann cells. The endoneurium contains glial cells, fibroblasts, and blood vessel capillaries. Multiple nerve fibers are bundled into fascicles. The fascicle is surrounded by a perineurium, which is a dense layer of collagenous connective tissue. The peripheral nerve is formed with multiple fascicles and is encircled by the epineurium, which is the outermost layer of the peripheral nerve and contains arteries, arterioles, and veins. The epineurium acts as a blood-nerve barrier and protects the nerve from local anesthetics and other chemical injuries [14].

INCIDENCE OF NEUROTOXICITY OF LOCAL ANESTHETICS

It is difficult to estimate the actual incidence of neurotoxicity of local anesthetics because many confounding risk factors lead to nerve injury during the perioperative period. In large prospective studies of peripheral nerve block, the incidence of neurological complications with peripheral nerve block is < 3%. Most of these complications are transient sensory deficits, and permanent nerve injury is rare [15-17]. Other studies on neurological complications with peripheral nerve block have shown that the risk of nerve injury is between 0.02% and 0.5%. The incidences of neurotoxicity of local anesthetics vary among studies because the estimation of the incidence of neurotoxicity of local anesthetics is influenced by the methods used to measure anesthetic-related neurological complications [16,17]. Urban and Urquhart estimated that the incidence of neurological deficits is 3–5% after a survey of the neurological deficits 2 weeks after a brachial plexus block. However, the incidence of neurological deficits beyond 4 weeks is only 0.4% [18]. There is a higher risk of prolonged paraesthesia after the administration of 4% articaine when than after the administration of other anesthetics [19,20]. Hillerup et al. [19] reported that 4% articaine causes neurosensory disturbances to two trigeminal branches. In addition, neurosensory disturbances associated with 4% articaine are related mainly to mandibular blocks.

RISK FACTORS FOR NEUROTOXICITY OF LOCAL ANESTHETICS IN DENTISTRY

The risk factors involved in the neurotoxicity of local anesthetics can be categorized into anesthetic and patient factors.

1. Anesthetic factors

Peripheral nerve block is an independent risk factor for the neurotoxicity of local anesthetics [21]. Additionally, the location of the injection influences the incidence of local anesthetic-induced peripheral nerve injury. A recent study has shown that local anesthetic-related peripheral nerve injury is most severe with intrafascicular injection

and lower with extrafascicular deposition. This suggests that the early direct exposure of nerve to a high concentration of local anesthetic can increase neurotoxicity [22,23].

Direct stimulation of the peripheral nerve with a needle during a local anesthetic injection can trigger direct nerve perforation and injury to the fascicle and perineurium. In addition, nerve injury is affected by the size and type of needle. A long-beveled needle is more likely to cause nerve punctures but more severe nerve injuries are caused by short-beveled needles [24].

High injection pressure of local anesthetics can increase the peripheral nerve injuries. Intraneural needle placement is indicated by a high injection pressure at the onset of injection, which leads to severe fascicular injury and persistent neurological deficits in dogs [25].

2. Patient factors

Patients with pre-existing neuropathies, such as diabetic peripheral neuropathy, Guillain-Barre syndrome, post-polio syndrome, and multiple sclerosis, are susceptible to local anesthetic-induced nerve injury [26]. In addition, all medical conditions that influence the microvasculature, such as peripheral vascular diseases, vasculitis, smoking, and hypertension, increase the vulnerability of nerves to ischemia and lead to an increase in local anesthetic-induced neurotoxicity during the perioperative period [22].

PATHOPHYSIOLOGY AND CELLULAR MECHANISMS OF NEUROTOXICITY OF LOCAL ANESTHETICS

Chemical nerve injury is caused by the toxicity of a solution or its additives. An in vitro study has shown that all local anesthetics have neurotoxic effects and the degree of neurotoxicity increases concentration-dependently [27]. The concentration of local anesthetics has decreased over time and the highest concentration of lidocaine and bupivacaine used currently is 2% and 0.5%, respectively. Studies that have investigated the toxicity of various local anesthetics have suggested that lidocaine is more toxic than equipotent concentrations of bupivacaine [28,29]. However, other studies have reported that there is no significant difference in toxicity among local anesthetics [27,30].

The vasoconstrictive effect of local anesthetics can aggravate nerve damage via ischemia and this damage can be aggravated further with adjuvant epinephrine. Vasoconstriction owing to local anesthetics with epinephrine prolongs the exposure of nerves to local anesthetics and reduces blood flow, which leads to a high risk of ischemic nerve damage [3]. After periods of ischemia, oxidative injury accompanied by reperfusion results in neuronal damage via the initiation of apoptosis.

The cellular mechanisms of local anesthetic-induced neurotoxicity have not been well clarified. Some studies have reported that DNA fragmentation, mitochondrial dysfunction, and endoplasmic reticulum calcium depletion are caused by local anesthetics. These processes result in the release of cytochrome c and activation of the caspase pathway, which leads to neuronal apoptosis [31-36]. The cellular mechanisms involved in local anesthetic-induced neurotoxicity include the intrinsic caspase, phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) pathways (Fig. 1). The voltage-gated sodium channel, a primary target of local anesthetics, and G-protein coupled receptors, a target for the systemic anti-inflammatory effect of local anesthetics, are unlikely to be involved in the pathophysiology of local anesthetic-induced neurotoxicity [37,38].

1. Intrinsic caspase pathways

Extrinsic and intrinsic caspase pathways play a central role in apoptosis. Werdehausen et al. [39] demonstrated that lidocaine induces apoptosis via cytochrome c release and apoptosis by lidocaine is strongly reduced by B-cell lymphoma 2 (bcl-2) overexpression and caspase-9 deficiency in the Jurkat cell line. This study suggests that lidocaine induces apoptosis via the activation of the intrinsic caspase pathway. The intrinsic caspase pathway

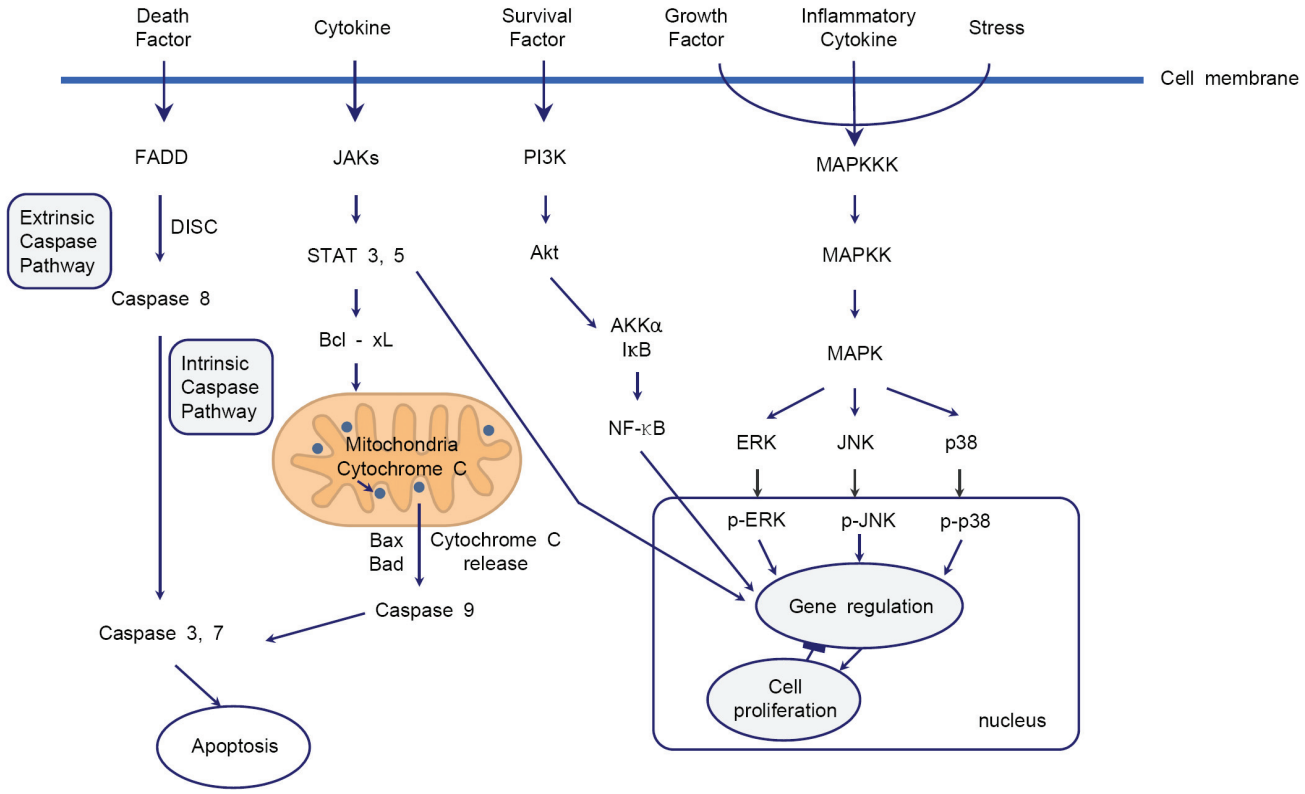

Fig. 1. Schematic diagram for the cellular mechanism of neurotoxicity of local anesthetics. The intrinsic caspase pathway, PI3K pathway, and MAPK pathway are reliable signaling pathways in the neurotoxicity of local anesthetics. Fas-associated protein with death domain (FADD); death-inducing signaling complex (DISC); phosphoinositide-3-kinase (PI3K); mitogen-activated protein kinase (MAPK).

is activated by the cytochrome c release and leads to cell apoptosis. The release of cytochrome c is offset by the activation of the bcl family [40].

2. PI3K pathway

The PI3K family is involved in an intracellular signaling pathway that promotes cell survival, growth, proliferation, and metabolism and angiogenesis. The activation of PI3K phosphorylates and activates serine-threonine protein kinase B (Akt), an enzyme for protection from apoptosis [41,42]. Some studies have investigated the relevance of the PI3K pathway in the neurotoxicity of local anesthetics. Ma et al. showed that pretreatment with dexamethasone significantly attenuates bupivacaine- and lidocaine-induced cell injury, prevents the decline in mitochondrial membrane potential caused by bupivacaine, and increases Akt phosphorylation. These protective effects of dexamethasone against bupivacaine-induced cell injury are suppressed by the pharmacological inhibition of Akt, which suggests that dexamethasone has a protective effect against bupivacaine-induced neuronal cell injury through the Akt signaling pathway [43]. In another study, it was shown that lithium attenuates bupivacaine-induced neurotoxicity through the activation of the PI3K/Akt pathway in mouse neuroblastoma cells [44].

3. MAPK pathway

Wang et al. [44] demonstrated that lithium provides a protective effect against bupivacaine-induced neurotoxicity via the activation of the extracellular signal-regulated kinase (ERK) signaling pathway. ERK is a member of the MAPK family. However, other studies have reported that the inhibition of p38 MAPK or ERK has a potential therapeutic effect against a chronic constriction nerve injury model, metabolic injury, and

excitotoxicity [45-47]. Haller et al. [48] showed that lidocaine-induced neurotoxicity is mediated by the specific activation of p38 MAPK but not that of ERK or c-Jun N-terminal kinase. In addition, the neuroprotective effect of p38 MAPK inhibitors decreases after more than 1 h of lidocaine administration, which suggests that lidocaine-induced neurotoxicity involves the specific and time-dependent activation of p38 MAPK.

CONCLUSIONS

It is difficult to discriminate the specific neurotoxic effect of local anesthetics because many factors can affect nerve damage during the perioperative period. In clinical settings, most nerve damages induced by local anesthesia are transient sensory defects and permanent nerve damage rarely occurs. However, permanent nerve damage can be fatal in a minority of patients with local anesthetic-induced permanent nerve damage. Therefore, it is essential to prevent local anesthetic-induced nerve damage. To prevent the neurotoxicity of local anesthetics, intrafascicular and high pressure injections should be avoided. Additionally, the use of the lowest effective concentration, the lowest effective volume, short-acting local anesthetics, and small needles is recommended. Finally, patients with comorbid, pre-existing neuropathies and vascular diseases require additional attention from their dentist regarding local anesthetic-induced nerve damage.

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