

A review of the mechanism of the central analgesic effect of lidocaine

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Abstract

Lidocaine, as the only local anesthetic approved for intravenous administration in the clinic, can relieve neuropathic pain, hyperalgesia, and complex regional pain syndrome. Intravenous injection of lidocaine during surgery is considered as an effective strategy to control postoperative pain, but the mechanism of its analgesic effect has not been fully elucidated. This paper intends to review recent studies on the mechanism of the analgesic effect of lidocaine. To the end, we conducted an electronic search of the PubMed database. The search period was from 5 years before June 2019. Lidocaine was used as the search term. A total of 659 documents were obtained, we included 17 articles. These articles combined with the 34 articles found by hand searching made up the 51 articles that were ultimately included. We reviewed the analgesic mechanism of lidocaine in the central nervous system.

Abbreviations: BK = bradykinin, CNS = central nervous system, DRG = dorsal root ganglion, EG = N-ethylglycine, GlyRs = glycine receptors, GlyT1 = glycine transporter 1, GPCRs = G-protein-coupled receptors, HCN = hyperpolarization-activated cyclic nucleotide-gated, iGluR = ionotropic glutamate receptor, *I_h* = inward current, IVL = intravenous lidocaine, KA = kainic acid, mGluR7 = metabotropic glutamate receptor subtype 7, NMDA = N-methyl-D-aspartic acid, VGSC/NaV = voltage-gated Na⁺ channel.

Keywords: G-protein-coupled receptor, intravenous administration, lidocaine, ligand-gated channel, mechanism, review, voltage-gated ion channel

1. Introduction

In 1943, Lofgren and Lundquist synthesized lidocaine, an amide local anesthetic, that has been used for local nerve block and epidural anesthesia for a long time since 1948. However, in the 1980s, it was widely recognized that intravenous lidocaine (IVL) can relieve peripheral neuropathic pain,^[1] hyperalgesia and complex regional pain syndrome.^[2] In recent years, studies on humans have shown that IVL is a useful strategy for general anesthesia. Perioperative IVL can reduce postoperative pain and improve postoperative prognosis.^[2,3] Lidocaine is one of the main drugs used for opioid-reduced anesthesia and opioid-free anesthesia.^[4] Lidocaine is the only local anesthetic approved for intravenous injection in the clinic, and the mechanism of its

analgesic effect has not been fully elucidated. In this paper, we summarized the recent literature on the analgesic mechanism of lidocaine.

Since this study is not a clinical study, but a review of basic research, it does not need the approval of the ethics committee. We searched for articles in the PubMed database by electronic search. The search period was from the 5 years before June 2019. The value of IF was more than 5, and the language restriction was English. Lidocaine was used as the search term. The search strategy was as follows: lidocaine AND (“last 5 years” [Pdat] AND Animals [Mesh:noexp]). A total of 659 documents were obtained. Two people evaluated the relevance and authenticity of the documents and identified 17 documents. A manual search identified 34 documents, and 51 references were ultimately included.

2. Effect of lidocaine on voltage-gated ion channels

The dorsal root ganglion (DRG), which contains first-order pain afferents, plays an important role in conveying peripheral nociceptive information to the central nervous system (CNS). DRG neuron ion channels are mainly voltage-gated ion channels, including sodium, potassium, and calcium channels. Lidocaine can block Na⁺ and K⁺ ion channels and regulate intracellular and extracellular calcium concentrations through other ligand-gated ion channels.

Lidocaine was the first sodium channel blocker to be identified. Its main mechanism of action is blocking voltage-gated Na⁺ channels (VGSC/NaVs). VGSC is considered as the main target of lidocaine,^[5,6] and lidocaine can reduce the peak currents of Na⁺ channels and accelerate the deactivation process to reduce the excitability of neurons and thus prevent or reduce the sensation of pain.^[6] The inhibition of high frequency discharge of excitatory

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cells largely depends on the prolongation of recovery time after VGSC inactivation. This prolongation may be due to the periodic binding of the drug to the high-affinity binding site during the action potential and then the slow separation of the drug from the site between action potentials (the “separation hypothesis”). The fast inactivation state represents the high-affinity binding state. In 1 study, lidocaine was found to be closely related to rapid deactivation.^[7] Lidocaine can also block potassium channel. In another study the whole-cell patch clamp method was used to measure DRG neurons. Lidocaine inhibited the instantaneous and sustained K^+ currents of DRG neurons and the excitability of postsynaptic neurons.^[8]

DRG neurons can be divided into 3 categories:

- (1) tetanic-firing neurons, which receive sensory information about pain and heat sensation^[9–11];
- (2) adapting-firing neurons; and
- (3) Single spike neurons (SSNs).

Whole cell-patch clamp of rat dorsal horn neurons showed that lidocaine (100 μ M) had an effect on the discharge characteristics of all 3 types of neurons, affecting the shape of the action potentials. VGSC partially blocked (the peak value of sodium current decreased by about approximately 50%); the same concentration of lidocaine could inhibited voltage-gated potassium channels in tetanic-firing neurons^[12,13]; thus, the different sensitivities of DRG ion channels could be exploited as a new method for blocking DRG differentiation. The resting potential of DRG neurons is determined by the balance of the delayed rectifier potassium channel and hyperpolarization-activated mixed inward current (I_h).^[14] The I_h is a mixed inward cation current mediated by hyperpolarization. In the open state, channels allows Na^+ and K^+ to pass through the cell membrane at a ratio of 1:3 to 1:5, showing nonselective permeability. The formation of an inward cation current in the nervous system, known as an I_h , increases the firing frequency of neurons and plays an important role in blocking spinal anesthesia. Lidocaine has reversible and dose-dependent inhibitory effects on the I_h of DRG neurons in rats.^[15] The inhibition of the I_h current by lidocaine may be related to hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels are special voltage-gated ion channel that mediates the I_h . Four subtypes, namely, HCN1–4, have been successfully cloned. Lidocaine has a nonselective effect on HCN channels and sodium channel currents of large and small DRG neurons at the same time. Lidocaine increase the membrane hyperpolarization and input resistance of HCN1 DRG neurons. At a concentration of 100 μ M, lidocaine was shown to significantly hyperpolarize the activation potential of HCN channel currents of large neurons but not those of small neurons.^[16]

In spinal and epidural anesthesia, the amount and speed of the drug spreading directly to the spinal cord are unpredictable.^[17] Spinal cord neurons are exposed to relatively high concentrations (such as 5–50 mM) of local anesthetics; whole IVL is used to treat neuropathic pain, and spinal cord neurons are exposed to much lower concentrations of local anesthetics than intrathecal anesthetics.^[18,19] The analgesic mechanism of intravenously administered lidocaine is more complicated than the simple blockade peripheral nerve impulses. The plasma concentration of lidocaine required to block peripheral nerve fiber pulses to a large extent (1–2 mg/kg) is much lower than the optimal concentration (ie, 4–20 μ M vs 300–800 μ M).^[20] Some studies have also shown that when a plasma concentration of lidocaine of 1 to 2 μ g/mL,

can inhibit the neuropathic pain in rats.^[21] A study on humans showed that the plasma concentration started at 1.0 μ g/mL and that the pain threshold under stimulation by ring finger pair currents (5 Hz) began to increase.^[18] Therefore, the analgesic effect of lidocaine cannot be explained by the theory of spinal ion channel blockade alone.

A study on the influence of lidocaine on the CNS above the spinal cord found that the pain threshold was increased and visceral pain was relieved after the injection of 0.5 μ L lidocaine into the ventral tegmental area,^[22] which was presumably related to the regulation of the dopaminergic system in the brain. The thalamus is the brain area related to the systemic effect of lidocaine. The mixed cation current I_h activated by the hyperpolarization of neurons in the thalamic cortex of rats is highly expressed in the thalamus. A potential target of lidocaine in the spinal cord of the CNS is the cation current I_h , which is activated by hyperpolarization. Whole-cell voltage- and current-clamp recordings of neurons in the ventral basal cortex of the thalamus were performed in vitro on brain slices from rats, and it was found that lidocaine significantly inhibited the I_h in rat thalamic cortical neurons in a concentration-dependent manner and that the effect of lidocaine was similar to the effect of sodium channel blockade.^[23] Lidocaine inhibits HCN1, HCN2, HCN1-HCN2 and HCN4 channel currents in *Xenopus laevis* oocytes and human embryonic kidney 293 cells, which may be related to the mechanism of systemic lidocaine delivered intravenously.^[24]

3. Effect of lidocaine on ligand-gated channels

Glutamate is the main excitatory neurotransmitter in the CNS.^[25] Glutamate receptors in the CNS include ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors. Metabotropic glutamate receptors are coupled with G proteins. iGluRs are the most representative ligand-gated channel receptors. iGluRs are important targets for drug development and can be categorized as N-methyl-D-aspartic acid (NMDA) receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainic acid (KA) receptors. A study showed that lidocaine inhibited the release of glutamate from the presynaptic terminals of the rat cortical terminals (synaptosomes),^[26] and inhibits the release of glutamate from the presynaptic terminals of spinal substantia gelatinosa neurons.^[20] Lidocaine pretreatment can reduce the activation of hippocampal microglia and the gene expression of the proinflammatory cytokines interleukin-1 β , interleukin-6, and tumor necrosis factor- α induced by KA. KA is similar to excitatory glutamate, so lidocaine can effectively treat brain injury related to glutamate excitatory toxicity.^[27] Kinase protein signaling pathways are involved in the regulation of glutamate release by lidocaine. Lidocaine (2 mM) significantly reduces the number of phosphorylated phosphorylated activated ERK-positive neurons induced by NMDA in the rat spinal dorsal horn and the number of phosphorylated activated ERK-positive neurons induced by α -amino-3-hydroxy-5-methyl-4-izoxazolepropionic acid.^[28] The P2X7 receptor plays an important role in pain regulation.^[29] Lidocaine can selectively inhibit the expression of the P2X7 receptor in *Xenopus* oocytes. It inhibits adenosine triphosphate-induced currents in P2X7 cells in a concentration-dependent manner. The maximum concentration for inhibition is 282 ± 45 μ mol/L.^[30] These results are helpful for understanding the mechanism of the analgesic effect of systemically and locally administered lidocaine.

Glycine receptors (GlyRs) are major inhibitory neurotransmitter receptors in the CNS of adult mammals.^[31,32] The intrathecal injection of strychnine, a GlyR antagonist, can cause hyperalgesia.^[33] Lidocaine can enhance the function of wild-type GlyR function at lower concentrations.^[34] When the S267 residue in the transmembrane domain of α 1-GlyRs is mutated, the potentiation of GlyR currents induced by lidocaine is abolished.^[34] The extracellular region of α 1-GlyRs is the site of action of lidocaine. The structure-activity relationship of anesthetics in its effect on α 1-GlyRs was further studied,^[35] and the results showed that loop 2 of α 1-GlyRs is the key region that mediates the regulation of lidocaine; this shows the commonality of the sites of action of isoflurane, lidocaine and ethanol and the importance of the allosteric regulation of the extracellular loop 2 region of α 1-GlyRs. Two-electrode voltage clamp electrophysiology showed that lidocaine enhances the glycine-induced chloride current in *Xenopus* oocytes.^[35]

Does intravenously administered lidocaine play a role through the glycine pathway to elicit its analgesic effect? As early as 1993, Biella and Sotgiu^[36,37] studied the interaction of systemic lidocaine on excitatory substances such as NMDA, strychnine and glutamic acid, which act on NMDA receptors, non-NMDA receptors and both, respectively. The results showed that systemic lidocaine blocked glutamate-induced responses of neurons in the spinal dorsal horn of rats and that this effect was blocked by strychnine.^[36] According to these results, the authors speculated that the GlyR,^[38,39] which is widely distributed in the spinal cord, may participate in the central inhibitory effect of systemic lidocaine. Glycine is not only the main inhibitory neurotransmitter in the spinal cord and brain stem but also a necessary costimulatory factor for NMDA-type excitatory glutamate receptors. The contribution of glycine to the analgesic effect of systemic lidocaine was further studied.^[40] A study showed that part of the analgesic effect of systemic lidocaine might be derived from the regulatory effect of lidocaine or its metabolites on the function of NMDA receptors. The inhibitory effect of lidocaine on NMDA receptors is consistent with the NMDA receptor-mediated effect on the development of chronic pain^[41] and is consistent with the temporary relief of such pain provided by lidocaine.^[42] The analgesic mechanism of intravenously administered lidocaine may be the action of lidocaine itself or its metabolite N-ethylglycine (EG).^[40,43] EG, which is a special substrate of the glycine transporter glycine transporter 1 (GlyT1), contains a glycine residue. It has a competitive inhibitory effect on the production of GlyT1, which at least partially mediates the analgesic effect of the systemically administered lidocaine. GlyT1 substrates such as EG are a promising strategy for the treatment of chronic pain.

4. Effect of lidocaine on G-protein-coupled receptor (GPCRs)

GPCRs can be divided into 3 groups: A, B, and C. The C group can be divided into 5 subgroups, including metabotropic glutamate receptor subtype 7 (mGluR7), gamma-aminobutyric acid (GABA) receptors and calcium receptors. mGluR7 stimulation facilitates pain responses.^[44-46] AMN082 is a selective mGluR7-positive allosteric modulator. In 1 study, lidocaine (15 μ g/0.2 μ L) was microinjected into the subthalamic nucleus of rats before AMN082 (2 nmol) was injected; the injection of lidocaine prevented AMN082 (2 nmol) from inducing excitation and reduced the duration of excitation. GABA_A receptor antagonists

can cause hyperalgesia, while GABA_A receptor agonists have the opposite effect.^[47,48] The effects of lidocaine (0.1–3 mm) on the expression of 122S-GABA_A and GABA_C in *X laevis* oocytes were detected by a 2-electrode voltage-clamp system. Lidocaine inhibited GABA_A receptor function at high concentrations (3 nM).^[34,49] In *Xenopus* oocytes, local anesthetics such as lidocaine have been shown to be selectively inhibit the Gq protein. The Gq protein is next to the Na channel and serves as an intracellular target of lidocaine; thus, the Gq protein may explain the effects that Na⁺ channel blockade cannot explain, such as GPCR-mediated pain and inflammation. Bradykinin (BK) is one of the most powerful pain-causing substances and important inflammatory mediators. There are 2 kinds of BK receptors, namely, B1 and B2. BK leads to spontaneous afferent nerve activity through the GPCR-B2 receptor and promotes central sensitization and ongoing pain. In *Xenopus* oocytes, lidocaine inhibits the response to BK in a time-dependent manner after incubation for 3, 5, or 10 minutes.^[50] There have been some reports about the effect of local anesthetics on to G α q/11 G protein GPCRs, such as substance P receptor neurokinin-1 receptor (NK-1R)^[51] and endothelin receptor, under the action of their respective endogenous agonists, substance P and endothelin 1, which are released in response to injury and contribute to postoperative pain. In the future, we will further explore the mechanism of the analgesic effect of lidocaine.

5. Conclusion

In summary, lidocaine acts on voltage-gated ion channels and ligand voltage-gated ion channels in neurons in the spinal cord or upper spinal cord, regulates the concentration of ions inside and outside cells, changes the transmembrane potential, regulates the excitability of neurons, and affects the discharge frequency and action potential conduction speed of nerve fibers. In addition, lidocaine target GPCRs and participates in many cell signal transduction processes, which not only explains the mechanism of its analgesic and antihyperalgesic effects but also may explain some of the other clinical effects of lidocaine, such as its neuroprotective, anti-inflammatory, and anticancer drug sensitization effects. In summary, there may be many mechanisms by which systemic lidocaine exerts its analgesic effect. The central role of systemically administered lidocaine in the spinal cord and upper spinal cord is consistent with its analgesic effect. The specific mechanism may need to be analyzed according to the nature of pain.

Author contributions

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References

- 1] Gozalo-Marcilla M, Gasthuys F, Schaulvliege S. Partial intravenous anaesthesia in the horse: a review of intravenous agents used to supplement equine inhalation anaesthesia. Part 1: lidocaine and ketamine. *Vet Anaesth Analg* 2014;41:335–45.
- 2] Weibel S, Jeltng Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev* 2018;6:CD009642.

- [3] McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs* 2010;70:1149–63.
- [4] Koepke EJ, Manning EL, Miller TE, et al. The rising tide of opioid use and abuse: the role of the anesthesiologist. *Periop Med (Lond)* 2018;7:16.
- [5] Lenkey N, Karoly R, Epresi N, et al. Binding of sodium channel inhibitors to hyperpolarized and depolarized conformations of the channel. *Neuropharmacology* 2011;60:191–200.
- [6] Scholz A. Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels. *Br J Anaesth* 2002;89:52–61.
- [7] Gawali VS, Lukacs P, Cervenka R, et al. Mechanism of modification, by lidocaine, of fast and slow recovery from inactivation of voltage-gated Na(+) channels. *Mol Pharmacol* 2015;88:866–79.
- [8] Komai H, McDowell TS. Local anesthetic inhibition of voltage-activated potassium currents in rat dorsal root ganglion neurons. *Anesthesiology* 2001;94:1089–95.
- [9] Lopez-Garcia JA, King AE. Membrane properties of physiologically classified rat dorsal horn neurons in vitro: correlation with cutaneous sensory afferent input. *Eur J Neurosci* 1994;6:998–1007.
- [10] Han ZS, Zhang ET, Craig AD. Nociceptive and thermoreceptive lamina I neurons are anatomically distinct. *Nat Neurosci* 1998;1:218–25.
- [11] Prescott SA, De Koninck Y. Four cell types with distinctive membrane properties and morphologies in lamina I of the spinal dorsal horn of the adult rat. *J Physiol* 2002;539:817–36.
- [12] Wolff M, Schnobel-Ehehalt R, Muhling J, et al. Mechanisms of lidocaine's action on subtypes of spinal dorsal horn neurons subject to the diverse roles of Na(+) and K(+) channels in action potential generation. *Anesth Analg* 2014;119:463–70.
- [13] Koplovitch P, Devor M. Dilute lidocaine suppresses ectopic neuropathic discharge in dorsal root ganglia without blocking axonal propagation: a new approach to selective pain control. *Pain* 2018;159:1244–56.
- [14] Mayer ML, Westbrook GL. A voltage-clamp analysis of inward (anomalous) rectification in mouse spinal sensory ganglion neurones. *J Physiol* 1983;340:19–45.
- [15] Bischoff U, Brau ME, Vogel W, et al. Local anaesthetics block hyperpolarization-activated inward current in rat small dorsal root ganglion neurones. *Br J Pharmacol* 2003;139:1273–80.
- [16] Zhou C, Ke B, Zhao Y, et al. Hyperpolarization-activated cyclic nucleotide-gated channels may contribute to regional anesthetic effects of lidocaine. *Anesthesiology* 2015;122:606–18.
- [17] Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. *Reg Anesth Pain Med* 2002;27:150–6.
- [18] Wallace MS, Dyck JB, Rossi SS, et al. Computer-controlled lidocaine infusion for the evaluation of neuropathic pain after peripheral nerve injury. *Pain* 1996;66:69–77.
- [19] Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. *Anesthesiology* 2000;92:1685–91.
- [20] Kurabe M, Furue H, Kohno T. Intravenous administration of lidocaine directly acts on spinal dorsal horn and produces analgesic effect: an in vivo patch-clamp analysis. *Scientific reports* 2016;6:26253.
- [21] Janig W. What is the mechanism underlying treatment of pain by systemic application of lidocaine? *Pain* 2008;137:5–6.
- [22] Ji NN, Kang J, Hua R, et al. Involvement of dopamine system in the regulation of the brain corticotropin-releasing hormone in paraventricular nucleus in a rat model of chronic visceral pain. *Neurol Res* 2018;40:650–7.
- [23] Putrenko I, Schwarz SK. Lidocaine blocks the hyperpolarization-activated mixed cation current, I(h), in rat thalamocortical neurons. *Anesthesiology* 2011;115:822–35.
- [24] Meng QT, Xia ZY, Liu J, et al. Local anesthetic inhibits hyperpolarization-activated cationic currents. *Mol Pharmacol* 2011;79:866–73.
- [25] Fonnum F. Glutamate: a neurotransmitter in mammalian brain. *J Neurochem* 1984;42:1–1.
- [26] Lin TY, Chung CY, Lu CW, et al. Local anesthetics inhibit glutamate release from rat cerebral cortex synaptosomes. *Synapse (New York, N Y)* 2013;67:568–79.
- [27] Chiu KM, Lu CW, Lee MY, et al. Neuroprotective and anti-inflammatory effects of lidocaine in kainic acid-injected rats. *Neuroreport* 2016;27:501–7.
- [28] Zhang L, Tanabe K, Yanagida F, et al. Different effects of local anesthetic on extracellular signal-regulated kinase phosphorylation in rat dorsal horn neurons. *Eur J Pharmacol* 2014;734:132–6.
- [29] Chessell IP, Hatcher JP, Bountra C, et al. Disruption of the P2X7 purinoceptor gene abolishes chronic inflammatory and neuropathic pain. *Pain* 2005;114:386–96.
- [30] Okura D, Horishita T, Ueno S, et al. Lidocaine preferentially inhibits the function of purinergic P2X7 receptors expressed in *Xenopus* oocytes. *Anesth Analg* 2015;120:597–605.
- [31] Dutertre S, Becker CM, Betz H. Inhibitory glycine receptors: an update. *J Biol Chem* 2012;287:40216–23.
- [32] Legendre P. The glycinergic inhibitory synapse. *Cell Mol Life Sci* 2001;58:760–93.
- [33] Sorkin LS, Puig S. Neuronal model of tactile allodynia produced by spinal strychnine: effects of excitatory amino acid receptor antagonists and mu-opiate receptor agonist. *Pain* 1996;68:283–92.
- [34] Hara K, Sata T. The effects of the local anesthetics lidocaine and procaine on glycine and gamma-aminobutyric acid receptors expressed in *Xenopus* oocytes. *Anesth Analg* 2007;104:1434–9.
- [35] Naito A, Muchhala KH, Trang J, et al. Manipulations of extracellular Loop 2 in alpha1 GlyR ultra-sensitive ethanol receptors (USERS) enhance receptor sensitivity to isoflurane, ethanol, and lidocaine, but not propofol. *Neuroscience* 2015;297:68–77.
- [36] Biella G, Sotgiu ML. Central effects of systemic lidocaine mediated by glycinergic receptors: an iontophoretic study in the rat spinal cord. *Brain Res* 1993;603:201–6.
- [37] Biella G, Lacerenza M, Marchettini P, et al. Diverse modulation by systemic lidocaine of iontophoretic NMDA and quisqualic acid induced excitations on rat dorsal horn neurons. *Neurosci Lett* 1993;157:207–10.
- [38] Basbaum AI. Distribution of glycine receptor immunoreactivity in the spinal cord of the rat: cytochemical evidence for a differential glycinergic control of lamina I and V nociceptive neurons. *J Comp Neurol* 1988;278:330–6.
- [39] van den Pol AN, Gorcs T. Glycine and glycine receptor immunoreactivity in brain and spinal cord. *J Neurosci* 1988;8:472–92.
- [40] Muth-Selbach U, Hermanns H, Stegmann JU, et al. Antinociceptive effects of systemic lidocaine: involvement of the spinal glycinergic system. *Eur J Pharmacol* 2009;613:68–73.
- [41] Schaible H.G. Peripheral and central mechanisms of pain generation. *Handb Exp Pharmacol* 2007;177:3–28.
- [42] Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain* 2000;87:7–17.
- [43] Werdehausen R, Mittnacht S, Bee LA, et al. The lidocaine metabolite N-ethylglycine has antinociceptive effects in experimental inflammatory and neuropathic pain. *Pain* 2015;156:1647–59.
- [44] Marabese I, Rossi F, Palazzo E, et al. Periaqueductal gray metabotropic glutamate receptor subtype 7 and 8 mediate opposite effects on amino acid release, rostral ventromedial medulla cell activities, and thermal nociception. *J Neurophysiol* 2007;98:43–53.
- [45] Palazzo E, Marabese I, de Novellis V, et al. Metabotropic glutamate receptor 7: from synaptic function to therapeutic implications. *Curr Neuropharmacol* 2016;14:504–13.
- [46] Palazzo E, Fu Y, Ji G, et al. Group III mGluR7 and mGluR8 in the amygdala differentially modulate nociceptive and affective pain behaviors. *Neuropharmacology* 2008;55:537–45.
- [47] Hwang JH, Yaksh TL. The effect of spinal GABA receptor agonists on tactile allodynia in a surgically-induced neuropathic pain model in the rat. *Pain* 1997;70:15–22.
- [48] Malan TP, Mata HP, Porreca F. Spinal GABA(A) and GABA(B) receptor pharmacology in a rat model of neuropathic pain. *Anesthesiology* 2002;96:1161–7.
- [49] Hollmann MW, McIntire WE, Garrison JC, et al. Inhibition of mammalian Gq protein function by local anesthetics. *Anesthesiology* 2002;97:1451–7.
- [50] Hamaya C, Barr T, Strichartz GR. Multiple inhibitory mechanisms of lidocaine on bradykinin receptor activity in model sensory neurons. *Reg Anesth Pain Med* 2018;43:605–12.
- [51] Li YM, Wingrove DE, Too HP, et al. Local anesthetics inhibit substance P binding and evoked increases in intracellular Ca²⁺. *Anesthesiology* 1995;82:166–73.