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Where and how do anaesthetics act? Mechanisms of action in the central nervous system

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Abstract

General anaesthesia is a balance of hypnosis, amnesia, analgesia, and immobility, including the inhibition of noxious autonomic reflexes. Local anaesthesia implements the latter two elements in a conscious patient. This review article discusses several important aspects of anaesthesia, beginning with basic concepts such as the minimum alveolar concentration and afterwards developing into a discussion about the mechanisms of action of anaesthetics on a cellular level, introducing electrophysiological investigations in the brain to study hypnosis and amnesia, in the dorsal horn of the spinal cord to study analgesia and the inhibition of noxious reflexes, and in the ventral horn of the spinal cord to study immobility, separately. In accordance with the results of electrophysiological patch clamp studies, researchers have confirmed that the modulation of neurotransmission input from dorsal afferent neurons into the dorsal horn of the spinal cord and effects on the spinal reflex arc from the dorsal horn to ventral horn motor neurons are important anaesthetic action mechanisms. Accordingly, intraoperative body movement of patients is not a sign of insufficient muscle relaxation, but rather insufficient analgesia. In conclusion, sufficient analgesia is a correct strategy (rather than muscle relaxant administration) for performing intraoperative patient immobility and for providing patients with good and safe intraoperative anaesthesia management by protecting them from noxious reflexes and stress including autonomic reactions such as hypertension and tachycardia.

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Key words: anaesthetics; anaesthetic action mechanism; analgesia; intraoperative; patient immobility

General anaesthesia is a balance of unconsciousness (hypnosis and amnesia), analgesia, and immobility including the inhibition of autonomic reflexes to noxious stimuli. Local anaesthesia implements the latter two elements in awake patients. The general purpose of anaesthesia is to prevent pain sensation and nociceptive reflexes during operations; that is, to block nociceptive transmission from peripheral tissue to the brain. Yet, how is patient immobility achieved during intraoperative anaesthesia management? Is the administration of muscle relaxant always necessary and correct to achieve intraoperative patient immobility? How are patients protected from noxious reflexes, such as hypertension or tachycardia due to activation of the sympathetic nervous system because of intraoperative manipulations, such as skin incision? In order to discuss these questions, we describe a review about where and how anaesthetics act in the central nervous system (CNS) introducing the studies investigating anaesthetic action mechanisms at a cellular level using the whole-cell patch clamp technique. At the beginning of this review article, we introduce briefly the principles of the whole-cell patch clamp technique as an important technique used for the study at a cellular level. Subsequently, we discuss action mechanisms of anaesthetics at a cellular level in order to confirm an appropriate and safe intraoperative anaesthesia management strategy.

WHERE DO ANAESTHETICS ACT IN THE CNS?

The CNS is composed of the brain and spinal cord. It is clear and indisputable that general anaesthetics act in the brain, as patients experience unconsciousness while under general anaesthesia. Yet, the spinal cord also plays a critical role in anaesthesia, despite the fact that most people, includ-

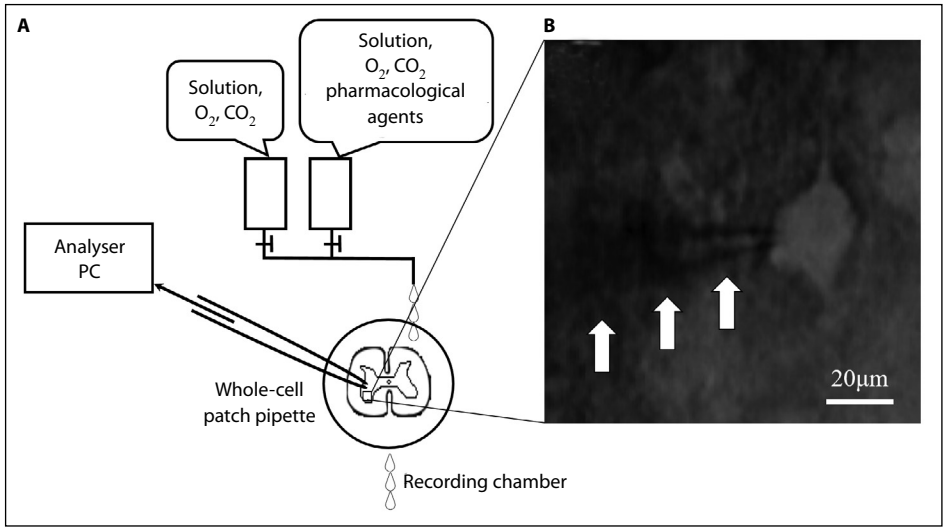

Figure 1. Schema of the patch clamp technique *in vitro*. The specimen slice is fixed on the stage of a recording chamber and perfused with artificial cerebrospinal fluid, with or without a dissolved pharmacological agent in order to investigate the pharmacological effects (**A**). A whole-cell patch pipette (↑) and a target motor neuron in the spinal ventral horn. The cell membrane surface is slightly hollow due to pressure from the nearby pipette tip (**B**)

ing many anaesthesiologists, still believe that the brain is the main site of action for general anaesthetics.

The minimum alveolar concentration (MAC) is an index of potency for volatile anaesthetics. The MAC is defined as the alveolar concentration of volatile anaesthetics needed to prevent body movement in response to a surgical pain stimulus in 50% of subjects. In other words, MAC is defined as the alveolar concentration of volatile anaesthetics necessary for patient immobility. This leads to the question as to what regions are responsible for patient immobility in response to intraoperative noxious stimuli. This fascinating and revolutionary question was answered more than 20 years ago [1] in research performed using goats attached to multiple cardiopulmonary bypass (CPB) machines, which allowed the head/brain and spinal cord/body to be anaesthetized with isoflurane separately. The MAC of isoflurane was measured in three different situations; situation 1 mimicked normal general anaesthesia (both the head and body were perfused with isoflurane); in situation 2, only the body was anaesthetized with isoflurane (only the CPB for the body was perfused with isoflurane); while in situation 3, only the head was anaesthetized with isoflurane (only the CPB for the head was perfused with isoflurane). Whereas the MAC of isoflurane was 1.2% in situations 1 and 2, this value more than doubled to 2.9% in situation 3. These results revealed that a much higher concentration of isoflurane was necessary for immobility when the spinal cord/body was not anaesthetized. Other research in rats reported similar differences in isoflurane MAC values when rats were anaesthetized in the same manner [2, 3]. Thus, spinal cord anaesthetic exposure is a more important determinant of MAC values than brain anaesthetic exposure, particularly because MAC values are defined by the anaesthetic's ability to prevent body movement [4].

THE PATCH CLAMP TECHNIQUE: ELECTROPHYSIOLOGICAL RESEARCH AND MECHANISMS RELATED TO ANAESTHESIA

Intracellular electrical activity can be measured using the patch clamp technique; Figure 1A shows a schema of this electrophysiological technique *in vitro*. Briefly, a slice of brain or spinal cord of approximately 500 μm in thickness is placed on the stage of a recording chamber and the slice is fixed with an anchor, perfused with artificial cerebrospinal fluid (aCSF) solution equilibrated with a gas mixture of 95% O_2 and 5% CO_2 (pH 7.4), and maintained at a temperature of 36°C [5]. A whole-cell patch pipette made from a pulled borosilicate glass capillary is filled with internal solution and attached to an analyser with a measuring electrode [5]. The patch pipette approaches to the target cell with a slight positive pressure at the tip. When the patch pipette is very close to the target cell (Fig. 1B), the slight positive pressure is removed so that the cell membrane surface is gently pulled into the pipette. As a result, the patch pipette tip becomes completely isolated and forms a high-resistance seal with the cell membrane in the 10–100 G Ω range ("gigaseal"). When the patch pipette is suctioned gently and momentarily in gigaseal, the cell membrane forms a tiny hole so that the internal solution and intracellular solution mix; this is known as a whole-cell patch [5]. Whole-cell patching enables the recording of action potentials from the target cell. The polarity of action potentials varies in accordance with the holding potential, which is adjusted to measure different target neurotransmitters and ion channels [5]. Pharmaco-

Table 1. Effects of anaesthetics on glutamate receptor-mediated excitatory neurotransmission and GABA/glycine receptor-mediated inhibitory neurotransmission in the brain

	Volatile anaesthetics	Xenon	N_2O	Midazolam	Opioids
AMPA	Excitatory transmission ↓[24]	↓ [6, 16,18]	↓ [21]		Excitatory transmission ↓ [20]
NMDA		↓ [6, 16,18]	↓ [19, 25]		
GABA	↑ [17, 22, 24]	(–) [6, 16,18]	(–) [25]	↑ [23]	
Glycine		(–) [6, 16,18]			

↑ augmentation; ↓ inhibition; (–) no effect; AMPA — α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA — N-methyl-D-aspartate GABA — γ-aminobutyric acid; NMDA — N-methyl-D-aspartate

logical agents, including anaesthetics, can be dissolved into aCSF to investigate actions or effects on target cells. Accordingly, the actions of anaesthetics can be measured directly using the patch clamp technique. For example, when a slice is perfused with aCSF containing an excitatory agonist (Fig. 1A), exogenous agonist-induced currents are recorded [5]. Washout when the exogenous agonist-induced current has returned to baseline completely, allows the slice to be perfused again with another aCSF solution. When the same exogenous agonist is used twice in sequence but induces smaller current the second time, this indicates a habituation or desensitization effect. In contrast, when the agonist-induced current becomes larger after the second application, this indicates a sensitization effect. Importantly, the ability of a pharmacological effect to "washout" is clinically significant as it indicates that the effect of the agent (e.g., an anaesthetic) is reversible [5]. Thus, for anaesthetic research, electrophysiological studies are used to confirm that exogenous agonist-induced currents return to baseline after washout and that anaesthetics produce identical effects after repeated treatment and washout. It is also of note that this technique may be applied to investigate effects of anaesthetics on synaptic transmission when combined with electrically evoked postsynaptic currents [5–7]. In recent years, the patch clamp technique has also demonstrated its utility *in vivo* [8–11].

NEUROTRANSMITTERS IN THE CNS

In the CNS, a balance of excitatory and inhibitory neurotransmission maintains nervous system function. Glutamate is the major excitatory neurotransmitter in the CNS. Glutamate binds several receptors, including ionotropic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, NMDA (N-methyl-D-aspartate) receptors, and kainite receptors [12, 13], as well as several metabotropic glutamate receptors. Major inhibitory neurotransmitters include GABA (γ-aminobutyric acid) and glycine[14], which also bind their respective cognate receptors. Anaesthetics typically inhibit excitatory neurotransmission and/or augment inhibitory neurotransmission, as we will explain in detail below.

Of note is that the pain pathway includes both ascending and descending components between the brain and the spinal cord that also use serotonin and noradrenaline as important neurotransmitters [15]. A discussion of these pathways was outside of the scope of the present review, as our goal was to overview anaesthetic action mechanisms in the brain and the spinal cord.

ACTIONS OF THE ANAESTHETICS IN THE BRAIN

Hypnosis and amnesia as components of anaesthesia are evidence that anaesthesia affects the brain. The above-described patch clamp technique has been used to investigate anaesthetic effects in different parts of brain, including the cortex cerebri [6, 16, 17], amygdala [18–20], hippocampus [21–23], and brainstem [24]. Volatile anaesthetics inhibit excitatory neurotransmission by acting on ionotropic glutamate receptors [24] and by augmenting inhibitory neurotransmission via GABA receptors [17, 22, 24] in the brain. Inhalational anaesthetics including xenon [6, 16, 18] and nitrous dioxide (N_2O or "laughing gas") [19, 21, 25] inhibit excitatory neurotransmission through AMPA and NMDA receptors without exerting effects on inhibitory neurotransmitter systems [6, 16, 18, 25]. Opioids similarly inhibit glutamate receptor-mediated excitatory neurotransmission in the brain[20], whereas the intravenous anaesthetic midazolam augments GABA receptor-mediated inhibitory neurotransmission in the brain [23]. A summary of these mechanisms is provided in Table 1.

ACTION OF ANAESTHETICS IN THE SPINAL CORD

The grey matter of the spinal cord is divided into ten laminae. Laminae I–VII are found in the dorsal horn, laminae VIII and IX are found in the ventral horn, and lamina X is equal to the grey commissure around the central canal (Fig. 2) [26]. The dorsal root only includes afferent fibres and transmits sensory information to downstream neurons. Therefore, the dorsal horn functions as a terminal of input fibres. In particular, lamina II (the *substantia gelatinosa*), where myelinated Aδ fibres and unmyelinated C fibres terminate, is considered as a critical location for the reception and modulation of nociceptive input [27–29]. The ventral

root contains efferent fibres, with the cell bodies of motor neurons in the ventral horn. Interneurons exist between afferent fibres and motor neurons, and input to the dorsal root is transmitted unidirectionally to motor neurons in the ventral horn as per Bell-Magendie's law (Fig. 2).

Volatile anaesthetics [7, 30, 31] augment inhibitory neurotransmission in the spinal cord dorsal horn via GABA receptors and glycine receptors. Volatile anaesthetics have been simultaneously reported to inhibit glutamate receptor-mediated excitatory neurotransmission in the spinal cord dorsal horn through GABAergic interneurons via a negative feedback mechanism on afferent input [7]. In contrast, xenon [6, 32] and N_2O [33] inhibit AMPA receptor- and NMDA receptor-mediated excitatory neurotransmission without having any effect on the inhibitory neurotransmission in the spinal cord dorsal horn [6, 31, 32]. Intrathecal midazolam produces analgesic effects [34], and is thought to augments GABA receptor-mediated inhibitory neurotransmission without affecting glycine neurotransmission [35]. Midazolam does not directly inhibit glutamatergic neurotransmission in the spinal cord, but does inhibit excitatory neurotransmission indirectly via GABAergic interneurons [36]. Intrathecal opioids produce or show strong analgesic effects [37, 38] by inhibiting glutamate receptor-mediated excitatory neurotransmission in the spinal cord [39, 40] without affecting GABA or glycine neurotransmission in the spinal cord dorsal horn [40] (Table 2). Finally, the local anaesthetic bupivacaine inhibits NMDA receptor-mediated neurotransmission in the spinal cord dorsal horn [41], even though local anaesthetics are essentially sodium channel blockers that suppress the spread of axonal excitation by preventing repolarization.

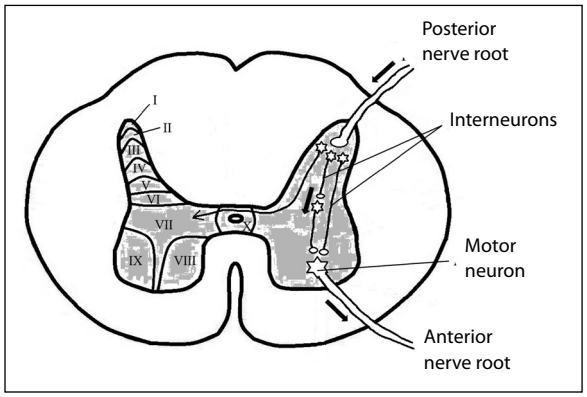

Figure 2. Transverse view of the spinal cord and Bell-Magendie's law. The grey matter of the spinal cord is divided into ten laminae [26]. The dorsal root contains only afferent fibres and transmits sensory information to downstream neurons. The ventral root contains only efferent fibres and the cell bodies of motor neurons are in the ventral horn. Interneurons exist between afferent fibres and motor neurons, and input into the dorsal root is transmitted unidirectionally to motor neurons in the ventral horn as per Bell-Magendie's law

Clinical studies suggest that the inhibition of spinal cord ventral motor neuron excitability by volatile anaesthetics [42, 43] and N_2O [43] is critical for anaesthesia-induced immobility during nociceptive stimulation. As briefly mentioned, volatile anaesthetics inhibit AMPA receptor- and NMDA receptor-mediated excitatory neurotransmission [44, 45] and augment glycine mediated inhibitory neurotransmission [46] in motor neurons of the ventral horn of the spinal cord. In the ventral horn, xenon inhibits AMPA receptor-mediated excitatory neurotransmission without affecting NMDA receptor-mediated excitatory neurotransmission in motor neurons [5], in contrast with its effects in the brain [6, 16, 18] and the dorsal horn of the spinal cord [6, 32] (Table 3). It has been reported that μ-opioid receptor agonists can modulate motor neuron excitability in, although opioids are not traditionally thought to affect motor function [47]. Lastly, the effects of N_2O and other intravenous anaesthetics on motor neurons in the ventral horn of the spinal cord are not yet well investigated, although some *in vivo* studies indicate that N_2O inhibits the activity of motor neurons [43, 48]. Anaesthetics may

Table 3. Effects of anaesthetics on glutamate receptor-mediated excitatory neurotransmission and GABA/glycine receptor-mediated inhibitory neurotransmission in the spinal cord ventral horn

	Volatile anaesthetics	Xenon
AMPA	↓ [44, 45]	↓ [5]
NMDA	↓ [44, 45]	(–) [5]
GABA		(–) [5]
Glycine	↑ [46]	(–) [5]

↑ augmentation; ↓ inhibition; (–) no effect; AMPA — α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA — N-methyl-D-aspartate; GABA — γ-aminobutyric acid

Table 2. Effects of anaesthetics on glutamate receptor-mediated excitatory neurotransmission and GABA/glycine receptor-mediated inhibitory neurotransmission in the spinal cord dorsal horn

	Volatile anaesthetics	Xenon	N_2O	Midazolam	Opioids
AMPA	↓ [7]	↓ [6,32]	↓ [33]	Excitatory transmission↓[36]	Excitatory transmission ↓ [39, 40]
NMDA	(–) [7]	↓ [6,32]	↓ [33]		
GABA	↑ [7, 30, 31]	(–) [6, 32]	(–) [31]	↑ [35]	(–) [40]
Glycine	↑ [7, 30, 31]	(–) [6, 32]	(–) [31]	(–) [35]	(–) [40]

↑ augmentation; ↓ inhibition; (–) no effect; AMPA — α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA — γ-aminobutyric acid; NMDA — N-methyl-D-aspartate

also affect neurotransmission between afferent fibres and motor neurons in the spinal could through direct effects on interneurons [49, 50].

As introduced in this chapter, anaesthetics have different mechanisms and sites of action in the spinal cord. Anaesthetics modulate the effects of nociceptive neurotransmission stimulation on the spinal reflex arc between the dorsal horn and ventral horn (Fig. 2) by inhibiting excitatory neurotransmissions and/or augmenting the inhibitory neurotransmissions in the spinal cord, without input from the brain. Suppression of the spinal reflex arc is the neural mechanism by which anaesthetic agents mediate immobility.

CONCLUSION

In this article, we have reviewed the mechanisms and sites of action for anaesthetics in the brain and spinal cord by introducing data from electrophysiological studies using the patch clamp technique. The modulation of input from dorsal afferent neurons into the dorsal horn of the spinal cord and suppression of the spinal reflex arc from the dorsal horn to the ventral horn motor are important mechanistic features of anaesthetics. Accordingly, the intraoperative body movement of patients is not a sign of insufficient muscle relaxation, but rather insufficient analgesia. Appropriate analgesic administration (rather than muscle relaxant administration) is a correct strategy for performing intraoperative patient immobility and for protecting patients from intraoperative noxious reflexes, stress, as well as autonomic reactions such as hypertension and tachycardia.

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