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Molecular Mechanism of General Anesthesia

Genel Anesteziklerin Moleküler Mekanizması

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ABSTRACT

Despite the widespread changes induced by general anesthetic agents, their exact effect sites are not clearly defined in the central nervous system (CNS). Recent molecular studies have pointed out specific sites in CNS on which anesthetic drugs show their effects. Hypnosis, amnesia, sedation are mediated by different receptors, neurotransmitters and neuronal pathways in the CNS. Protein base theory of anesthesia, which focuses on ion channels, took the place of lipid-based theory in the 1980's. There are two types of receptors, which are known to be responsible for the general anesthetic action: neurotransmitter receptors and ion channels. Background channels are also described as targets for anesthetic action. Enhancement and block of TWIK Related K^+ channels (TREK), TWIK related arachidonic acid activated K^+ channel (TRAAK), and TWIK related acid-sensitive K^+ channels (TASK) channels have been reported at low concentrations of volatile anesthetic agents. Two-pore-domain potassium channels are protein complexes embedded in cell membranes. They selectively allow potassium ions to pass through the cellular membrane. These channels are also capable of changing the membrane potential by means of neuronal excitability, neurotransmitters and hormone secretion. Of those channels, TASK-1 and TREK-1 are activated by volatile anesthetic agents. In this article, receptors responsible for anesthesia in CNS and their mechanism of action will be reviewed.

Keywords: General anesthesia, molecular pharmacology, consciousness

ÖZ

Genel anestezik ajanlar, nörotransmitterleri modüle ederek santral sinir sisteminde yaygın nöronal değişime neden olmaktadır. Yeni yapılan moleküler araştırmalarda anestezik ajanların etki ettiği spesifik alanlar üzerinde durulmaktadır. Hipnoz, amnezi, sedasyon santral sinir sisteminde farklı reseptör, nörotransmitter ve nöronal yolaklar aracılığıyla sağlanır. 1980'lerin başında yapılan çalışmalar sonrasında, iyon kanallarına odaklanan protein temelli anestezi teorisi, lipid temelli anestezi teorisinin yerini almıştır. Protein temelli teoriye göre, genel anestezik etkiden sorumlu iki tip reseptör mevcuttur; nörotransmitter reseptörler ve iyon kanalları. "Background" iyon kanalları da anestezik etki için yeni tanımlanmış hedef reseptörlerdir. İki porlu (two-pore-domain) potasyum kanallarından TWIK ilişkili K^+ kanalı (TREK), TWIK ilişkili araşidonik asitle aktive K^+ kanalı (TRAAK), TWIK ilişkili asit duyarlı K^+ kanalları (TASK) tipteki kanalların volatil ajanların düşük konsantrasyonunda güçlendiği ya da bloke olduğu bildirilmiştir. İki porlu potasyum kanalları, biyolojik membranlarda bulunan protein komplekslerdir. İki porlu potasyum kanalları, potasyum iyonları için özeldir ve potasyumun hücre membranından geçmesine izin verirler. İki porlu potasyum kanalları, nöronal uyarılma, nörotransmitter ve hormon salınımı yoluyla, membran potansiyelindeki değişikliklerden de sorumludurlar. İki porlu potasyum kanalların TASK-1 ve TREK-1 alt tipleri volatil anestezik ajanlarla (örneğin, izofluran, kloroform, dietil eter) uyarılır. Bu makalede santral sinir sisteminde bulunan ve genel anesteziklerin etkisinden sorumlu reseptörler ve bunların etki mekanizmaları gözden geçirilecektir.

Anahtar Kelimeler: Genel anestezi, moleküler farmakoloji, bilinç

INTRODUCTION

Our understanding of mechanisms involving the conduct of general anesthesia has improved in recent years. Some specific sites within the central nervous system as the target of the anesthetic agents have been introduced. Hippocampus has been shown to be responsible for the amnestic effects, neo cortex and thalamus were found to be related with sedation, and hypothalamus was thought to be the site responsible for the hypnotic action (1). Hypnosis, amnesia and sedation are mediated by different receptors, neurotransmitters and neuronal pathways in the central nervous system (CNS).

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Protein base theory of anesthesia, which focuses on ion channels, took the place of lipid-based theory in the 1980's.

Recent studies again have been focusing on the anesthetic's effect on lipid membranes. Anesthetics have been shown to disrupt lipid ordered membranes, and shift their melting temperature (2-9).

RECEPTORS

There are two types of receptors, which are known to be responsible for the general anesthetic action: neurotransmitter receptors, and ion channels.

1. Neurotransmitter receptors (10)

a. Ligand gated receptors (ionotropic receptors)

These are excitatory or inhibitory in nature according to the neurotransmitter that binds to it. Ligand gated receptors have got two domains. The first one has got a trans-membrane domain. It functions as a channel. The other one, which has got ligand-binding sites, is extracellular (11).

Examples of ligand-gated receptors are nicotinic acetylcholine receptors, 5-HT3 receptors, gamma-aminobutyric acid type A (GABA-A) receptor, glutamate (ionotropic) receptors, glycine receptors, and purinergic receptors.

b. G protein-coupled receptors (metabotropic receptors)

Binding to this metabotropic type of receptors changes the structure and causes the activation of G protein. Then generation of messengers such as cAMP, cGMP, diacylglycerol or calcium is controlled. At the end of the process G protein is inactivated by GTPase enzyme.

Metabotropic glutamate receptors, muscarinic acetylcholine receptors, GABA-B receptors, most of the serotonin receptors, and receptors for epinephrine, norepinephrine, dopamine, histamine, neuropeptides and endocannabinoids are the examples of G protein-coupled receptors (12).

2. Neurotransmitter receptors

GABA receptors: GABA is the major inhibitor receptor in the CNS. GABA receptor has five subunits (α, β, γ, δ, and ε) which cluster to compose a chlorine channel. The most frequently encountered receptor combinations are α1 β2 γ2 (60% of GABA α receptors), α1 β3 γ1 and α3, βn γ2 (13,14). Volatile anesthetic agents and barbiturates have an agonistic effect on GABA-A receptors whereas ketamine has an antagonistic effect on GABA-A receptors (15-17).

Glycine receptors: Glycine receptors are inhibitory receptors located in the CNS, but predominantly in the spinal cord. The receptor is composed of five subunits (3α and 2β). Its function resembles that of the GABA-A receptors and once the inhalation anesthetics bind to glycine receptors in the spinal cord the inflow of chloride ions into the cells is enhanced, the result is loss of response to a painful stimulus (18,19). The minimal alveolar concentration (MAC) value of volatile anesthetic agents is increased when glycine receptors are blocked. They are responsible for the 20-55% of isoflurane-mediated immobility, and 20% of halothane-induced immobility (20,21).

Nicotinic acetylcholine receptors (nAChR): These receptors control the synaptic conduction in CNS. Once activated, the resulting excitatory postsynaptic currents (EPSCs) lead to the cellular cation inflow. Low concentrations of general anesthetics display suppressive action on nAChR by blocking EPSCs. (22). Propofol inhibits human neuronal α3β2 and α7 nAChR subtypes expressed in oocytes (23).

Glutamate receptors: These receptors are the dominant excitatory neurotransmitter of the CNS. It acts via metabotropic (pre-synaptic) and ionotropic (post-synaptic) receptors. Ionotropic glutamate receptors are NMDA, AMPA, and kainate. Nitrous oxide, xenon and ketamine are glutamate receptor antagonists with high potency (21,24). Ionotropic glutamate receptors generate EPSCs by leading the inflow of the cation as well. Volatile anesthetic agents block excitatory neurotransmission by both inhibiting postsynaptic glutamate receptors and releasing glutamate from the presynaptic area (25,26). Isoflurane has been shown to inhibit GLuR6 kainate receptor subunits at medullary level, thereby increasing the MAC of anesthetic agents. AMPA receptors and different subunits have been found to be responsible for the Xenon's ability to induce immobility (21,24,27).

Serotonin receptors: Serotonin receptors are responsible for the cation conductance which leads to membrane depolarization and neuronal excitation. The main member of this receptor family is the serotonin subtype of 5-HT3. The activation of serotonin receptors by halogenated anesthetic agents, and inhibition by barbiturates or ketamine results in an altered state of consciousness (21,28). Experimental studies, which have been given specific serotonin capture inhibitors in determined cerebral nuclei, have reported an increase in MAC necessary for immobility.

3. Ion channels

a. Potassium channels: Potassium channels are activated by volatile agents and ketamine, as a result the transport of potassium ions is increased, cell membrane is hyperpolarized, and neuronal activity is inhibited (29,30).

b. Sodium channels: Volatile anesthetic agents inhibit presynaptic voltage-gated sodium channels located in the glutamatergic synapses. Therefore, the release of presynaptic neurotransmitters is blocked and neuronal activation is inhibited (31).

4. Background channels

Background channels are also described as targets for the action of the anesthetic agents. The action of TWIK Related K^+ channels (TREK), TWIK related arachidonic acid activated K^+ channel (TRAAK), and TWIK related acid-sensitive K^+ channels (TASK) channels is enhanced and blocked at low concentrations of volatile anesthetic agents (32).

Two-pore-domain potassium channels (K2p): Potassium channels are protein complexes embedded in the biological membranes. They are selectively permeable to potassium ions and allow potassium to pass through the cellular membrane. Two-pore-domain potassium channels are also responsible for the changes of the membrane potential by means of neuronal excitability, neurotransmitters and hormone secretion. There are four different types of K2p channels, Tandem of pore domains in weak inward rectifying K^+ channel (TWIK)-1, TWIK-2, TREK-1, and TRAAK. Volatile anesthetic agents (e.g. isoflurane, chloroform, diethyl ether) activate two of those K2p channels, TASK-1 and TREK-1 (32-38). TREK-1 is an inhibitory mechanoreceptor or an inhibitory effector. Once activated, TREK-1 inhibits neuronal firing by hyperpolarizing the cell (39).

It has recently been shown that volatile anesthetics activate phospholipase D2 (PLD2) by disruption of palmitate-mediated localization and substrate presentation causes anesthetic sensitivity in TREK-1 (4). The PLD2 appears to be an important factor for understanding the regulation of TREK-1. Transferring the PLD2 binding site to it could transfer the anesthetic sensitivity to an anesthetic insensitive channel TRAAK. However, the reason as to why anesthetic induced expansion by anesthetics lead to PLD2 translocation is not clear. The suggested mechanism of action is dependent on the affinity of PLD2 to the carboxyl C-terminal in TREK-1 (39).

The role of anesthetics on lipid membrane: Physiological role of the TREK-1 receptor in anesthesia has been clarified (32,40,41). This receptor's anesthetic action depends on the lipid membrane. This dependence has led us to think that the lipid cell membrane may be a target for anesthetic agents. It has also been shown that anesthetic sensitivity could be transferred to an insensitive channel TRAAK by means of PLD2. Therefore it is suggestive that this effect may be transferable (4). The nicotinic acetylcholine receptor (PA activates), GABA-A receptor and NMDA (PIP2 regulates) are other channels which have anesthetic action potential by disruption of lipid regulation (42-44).

Anesthetic agents have activating action on mechanical channels whereas they both activate and inhibit anesthetic sensitive membrane channels. However, most of the anesthetic agents inhibit excitatory channels but activate inhibitory channels. Inhibitory channels are generally neurotransmitter-gated in nature (45). An intermediary structure such as a lipid would be an explanation for this opposite effect.

CONCLUSION

General anesthetic drugs are used for inducing unconsciousness. They have been traditionally known as nonspecific drugs with their widespread effects. However, recent molecular pharmacology studies have shown selective receptors and structures in CNS, which are modulated by specific anesthetics and as a result inducing unconsciousness. Future treatment modalities in medicine focus on molecular receptors for patient based specific therapies. Molecular explorations on effects of general anesthetics will be more precise for performing patient based anesthesia.

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