Stunning the neural nexus: Mechanisms of general anesthesia

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General anesthesia requires managing a complex array of anesthetic agents that act on an intricate web of neural connections or neural nexus. Both inhaled and intravenous anesthetics must intervene at some level of the neural nexus that provides for amnesia, immobility, hypnosis, and suppression of noxious reflexes. These interactions occur at the spinal and supraspinal level and involve spinal pathways and centers of arousal and memory formation centrally.

Current research does not support the notion of a unitary mechanism of action for general anesthetics, but rather that anesthetics act by altering neuronal ion channels and neural communication. In general, anesthetics act by either enhancing inhibitory transmission or blocking excitatory conduction in neural impulses. The potent inhaled agents and most intravenous agents enhance the inhibitory λ-aminobutyric acid subtype A ($GABA_A$) and glycine channels and depress the excitatory neuronal nicotinic acetylcholine (nnACh) receptors. Nitrous oxide and ketamine act primarily by depressing the excitatory N-methyl-D-aspartate (NMDA) receptors and enhancing the opioid μ receptors. The extent, distribution, and subunit composition of these receptors determine the effects of various anesthetic agents on an individual patient. This variability, both within the patient and among the mechanisms of action of anesthetics, provides a reasonable degree of flexibility to the clinical practice of anesthesia.

Key words: **General anesthesia, ion channels, theories of anesthetic action.**

In order to induce general anesthesia, the anesthetist draws on an armamentarium that provides for an assortment of neurological effects: amnesia, analgesia, loss of consciousness, muscle relaxation, and suppression of noxious reflexes.[1] However, these components of neural function are widely dispersed within the central nervous system (CNS), and the drugs that provide these elements of anesthesia have variable profiles regarding their effects. For example, blockade at the level of the spinal cord can provide analgesia and immobility in response to noxious reflexes, but only interventions within the brain can bring about amnesia and hypnosis. In fact, minimum alveolar concentration (MAC), as measured by the absence of movement to noxious stimuli, is defined by the spinal, not supraspinal, contribution to the anesthetic state. The traditional 3-neuron models of the spinothalamic tract (pain and temperature) and posterior columns (touch and proprioception) allow modification at both presynaptic and postsynaptic sites within the pathways and via a variety of neurotransmitters.

At the supraspinal level, the reticular formation in the brainstem processes sensory information before it continues to the hypothalamus, thalamus, and cortex; further, midbrain reticular neurons play a key role in the control of arousal and consciousness. Neurons within the hippocampus, which plays a critical role in new memory formation, are subject to input from an array of other CNS neurons. This implies that general anesthesia may require actions at different neural sites and via different molecular mechanisms.[2,3] Thus, the anesthetist is faced with pharmacologically manipulating an elaborate web of neural connections, or neural nexus, in order to achieve general anesthesia.

There is international agreement that the investigation of the mechanism of general anesthetics must include (1) defining the clinical endpoints of these agents, (2) identifying the neuronal networks involved in achieving these endpoints, (3) characterizing each network with regard to its biomolecular function, and (4) exploring the integration of these networks.[4] This article will review the basic neurophysiology underlying communication within the CNS and discuss the neural networks and cellular mechanisms currently believed to support the actions of the intravenous and inhaled anesthetics.

Defining clinical anesthesia

Specific components of anesthesia are not generally agreed on; amnesia and immobility are typically expected outcomes, while unconsciousness, analgesia, and suppression of reflexes to noxious stimuli are apparently debatable.[5] Among patients who request

general anesthesia, it is clear that they do not wish to recall anything about the surgical event. Undoubtedly the surgeon requires immobility in order to accomplish his task. However, many patients also would prefer to be unconscious during surgery, and many surgeons prefer this scenario as well. If one accepts unconsciousness as requisite to the anesthetized state, then analgesia is no longer a necessary stated component. This is because pain is the conscious awareness of a noxious stimulus and therefore cannot be perceived in the unconscious patient.[5] Most practitioners would agree, however, that the suppression of noxious reflexes and analgesia are beneficial to the patient. Cardiovascular responses to surgical stimuli can occur in the absence of movement and may be harmful to a subset of patients, while analgesics may obtund these responses and provide for pain relief well past emergence.

• *Unconsciousness.* The neuronal correlates of consciousness are as yet under discussion, but there is reasonable consensus that certain aspects of consciousness (eg, pain, visual awareness, self-consciousness) employ a common mechanism.[6] The networks involved in consciousness and arousal include the cerebral cortex, thalamus, and reticular formation. These areas have a high density of receptors important to anesthesia including γ-aminobutyric acid, subtype A ($GABA_A$), N-methyl-D-asparate (NMDA), and acetylcholine (ACh) receptors. These cortical receptors also are subject to input from subcortical arousal systems.

• *Amnesia.* Key areas involved in memory formation include the hippocampus, amygdala, and prefrontal cortex.[5] Implicit memory is information that is recalled unconsciously, while explicit memory is recalled by a deliberate, conscious effort. Blocking implicit memory is a target of anesthesia. Both of these memory pathways use NMDA and non-NDMA receptors that respond to the neurotransmitter glutamate and serotonergic interneurons.[7]

• *Immobility.* Lack of a motor response to a noxious stimulus must involve blunting the simple withdrawal reflex mediated within the spinal cord. Blunting this response necessarily decreases the ascending transmissions to the brain that elicit arousal reflexes.[3,5] Within the spinal cord, both sensory and motor neurons are targets of anesthetics. Spinal dorsal horn neurons are inhibited in a dose-dependent fashion by some general anesthetics, which also depress the excitability of spinal motor neurons. Spinal reflexes involve $GABA_A$ receptor and the glutamate receptors for NMDA, α-amino-5-methyl-3-hydroxy-4-isoxazole propionic acid (AMPA), and kainite.

• *Analgesia.* Nocioceptive impulses are transmitted in the spinal cord, therefore, an expected target of anesthesia includes blunting nocioception at this level. Analgesia is a property of some anesthetics but not others.[5,8] Some agents are hyperalgesic at very low concentrations, such as 0.1 MAC, but become analgesic at 0.4 to 0.8 MAC.[9] Blocking ascending nocioceptive impulses can occur at the level of glutamate, GABA, or μ receptors within the spinal cord.

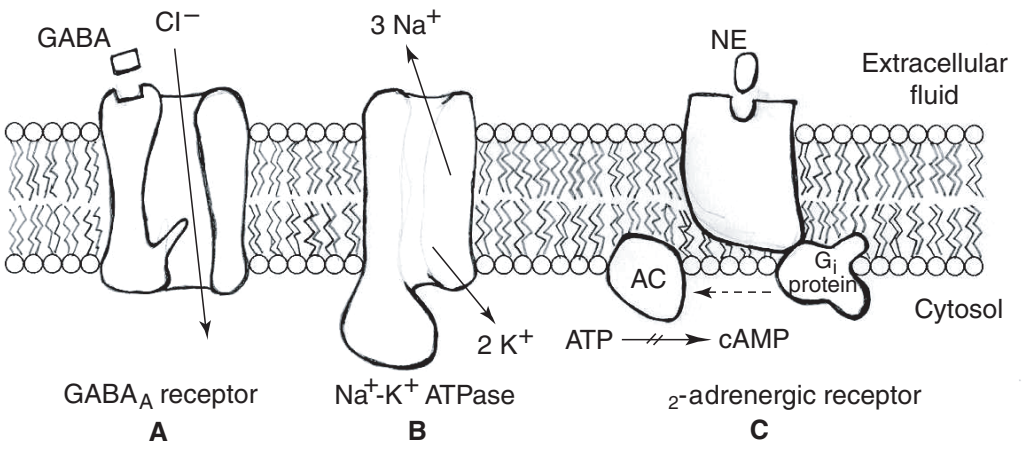
Characterization of general anesthesia mechanisms

The Meyer-Overton correlation has historically been used to hypothesize the mechanism of volatile anesthetics. It is based on an almost linear relationship between an anesthetic's potency and its lipid solubility.[10] This property originally suggested a unitary mechanism of action in which a critical concentration of anesthetic occupies hydrophobic or lipophilic regions of neuronal lipid membranes, altering neural function. However, the Meyer-Overton hypothesis has failed to be fully supported as a unitary mechanism by modern research.[2,11-13] Exceptions to the Meyer-Overton rule include: (1) the high variability of anesthetic potency between isomers with similar oil/gas partition coefficients (MAC of isoflurane vs enflurane); (2) certain agents expected to act as anesthetics, which instead have the ability to elicit convulsive activity; and (3) the identification of highly lipid soluble agents that are nonanesthetics.

Despite these issues, Meyer-Overton correlations with anesthetic action have been observed at many levels of CNS integration including molecular (ion channels), subcellular (single neuron action potentials), cellular (firing rate of neurons), microcircuit (depression of spontaneous firing), system (block of somatosensory evoked potentials), and brain (cerebral concentration of anesthetic).[4] One recent model supports the role of anesthetic solubilization within the neuronal membrane causing a redistribution of lateral pressures that alters the conformation of the membrane proteins.[10] Overall, though, current theoretical and empirical evidence suggests that anesthetics act on a multitude of hydrophobic sites within the neural membrane and that these sites are protein structures that form ion channels.[13,14]

Questions remain regarding the exact nature of inhaled anesthetic-protein interactions: anesthetic gases are characterized by low affinity interactions with extensive effects. Their kinetics may be described as partitioning into, rather than binding to, membrane proteins.[15] Data suggests that inhaled anesthetics alter membrane protein function by interacting at the lipid bilayer-protein channel interface. Weak electrostatic

Figure 1. Model of neuronal phospholipid bilayer*



Model of ligand-gated ion channel (A) membrane pump (B) and G-protein linked receptor (C) within a cell membrane. In a ligand-gated ion channel, such as a $GABA_A$ receptor (A), binding of GABA opens the channel so that chloride ions can enter the neuronal cell, hyperpolarizing it. B depicts the Na^+-K^+ membrane pump, with its intrinsic ATPase activity that couples the translocation of 3 Na^+ molecules out of the cell and 2 K^+ molecules into the cell to the energy of ATP hydrolysis. C illustrates an α_2-adrenergic receptor coupled to G_i protein whose activation inhibits the adenylyl cyclase enzyme within the cell membrane.

* GABA indicates γ-aminobutyric acid; Cl^-, chloride ion; Na^+, sodium ion; K^+, potassium ion; ATP, adenosine triphosphate; NE, norepinephrine; AC, adenylyl cyclase; G_i, guanosine inhibitory protein.

forces may play a role in addition to hydrophobic nature of the interaction site.

Because neural function is predicated on the conduction of electrical impulses (action potentials) that result from the altered conductance of ions through membrane channels, and the structure of these channels is well delineated, the search for a mechanism of action has productively extended here.[11,13,16] Within this premise, general anesthesia may be approached with the view that its components can be most effectively balanced by attending to the most efficacious combination of agents based on their molecular site of action.

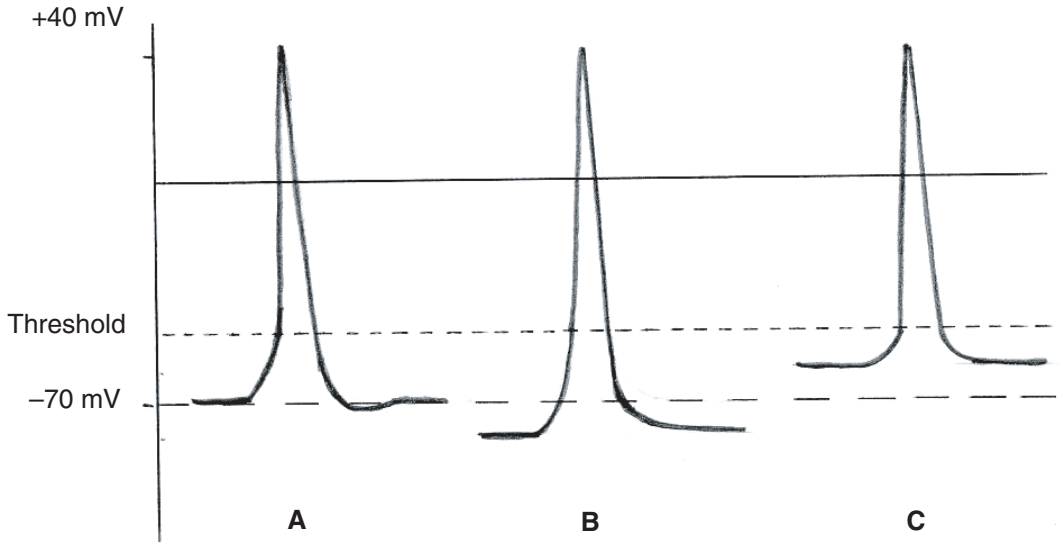
Neural communication

Within the neural nexus, the movement of sensory information into conscious perception requires 2 processes: propagation of information along a single neuron and communicating this information across a very small interneuronal space or cleft to other neurons. Propagation along a single neuron is an electrical process that occurs in the form of action potentials, while communication between neurons is a chemical process that occurs across a synaptic cleft between the presynaptic and postsynaptic nerve terminals. Requisite to understanding the mechanism of action of general anesthesia is a basic understanding of neuronal cell membrane structure, the generation of action potentials, and synaptic function.

• *Voltage-gated ion channels.* Neuronal cell membranes consist of a phospholipid bilayer that is packed with various proteins that serve as ion channels, membrane pumps, and/or hormone receptors (Figure 1). Membrane pumps, for example, provide for the electrical and chemical balance across the membrane, maintaining conditions satisfactory for normal cellular function. Neuronal axons exhibit a distinct permeability to K^+, creating a resting membrane potential of approximately –70 millivolts (mV). That is, the inside of the cell membrane is negative with respect to the outside, and the difference in voltage between the outside and inside of the membrane is 70 mV. In order to maintain this resting potential, Na^+-K^+ ATPase (a membrane-bound enzyme coupled to ATP hydrolysis) pumps 3 Na^+ out of the cell for every 2 K^+ pumped in. This mechanism not only sustains the negative charge of the inner membrane but also contributes to the relatively high concentration of Na^+ and low concentration of K^+ in the extracellular fluid. In response to a depolarizing influence that decreases the membrane potential to threshold, a brief dramatic opening of voltage-gated Na^+ channels occurs, which results in an action potential (Figure 2).

Repolarization occurs due to a brief opening of a

Figure 2. Graphic depiction of neuronal action potential



Resting membrane potential is –70 mV. (A) This indicates normal action potential. The upstroke is the result of a rapid influx of Na^+ ions (depolarization); the downstroke is due to an influx of K^+ ions (repolarization). (B) Resting membrane potential has increased to –80 mV, creating a state of hyperpolarization and making it more difficult for the neuron to reach threshold. (C) Resting membrane potential has decreased to –60 mV, increasing the probability of reaching the threshold for firing.

voltage-gated K^+ channel. Clinical concentrations of general anesthetics interfere minimally with these voltage-gated Na^+ channels and therefore could interfere with action potential generation.[17,18] A class of K^+ channels known as K^+ leak channels is stimulated by volatile anesthetics and may contribute to neuronal hyperpolarization.[19]

Voltage-gated Ca^{2+} channels play a significant role in neurotransmitter release from the presynaptic nerve terminal. As the presynaptic terminal is depolarized, Ca^{2+} channels open and Ca^{2+} enters the terminal. The influx of Ca^{2+} triggers exocytosis of neurotransmitter (NT) containing vesicles, releasing the NT into the synaptic cleft. Among the voltage-gated ion channels, Ca^{2+} channels exhibit the most sensitivity to general anesthesia, but at 1 MAC of halothane, Ca^{2+} channel function is only 20% inhibited.[13] Current evidence does not support a role for the voltage-gated Ca^{2+} channels in anesthesia-induced hindering of axonal conduction or synaptic transmission.

• *Control of neurotransmission.* Converging influences within the neural nexus can substantially alter communication between neurons. These influences occur primarily via presynaptic inhibition or facilitation and postsynaptic inhibition of the synaptic membranes. These mechanisms serve to either hyperpolarize the neural membrane, making it more difficult to trigger an action potential (see Figure 2B), or depolarize the membrane, increasing the probability of triggering an action potential (see Figure 2C).

At least 3 mechanisms of presynaptic inhibition have been identified. In one, a mediating neuron influences the presynaptic nerve terminal to close its Ca^{2+} channels, decreasing its ability to release NT. In a second mechanism, activation of ligand-gated receptors can directly inhibit NT release, independent of Ca^{2+} influx; this is the mechanism of action of botulinum and tetanus toxin. A third method of hyperpolarizing the presynaptic terminal is to activate $GABA_A$-gated Cl^- channels, enhancing the flow of Cl^- into the cell and increasing the membrane potential. In addition, there is evidence that a background K^+ current ($I_{K(An)}$), when activated by volatile anesthetics, hyperpolarizes neurons at both presynaptic and postsynaptic sites thereby contributing to the anesthetic state.

Presynaptic facilitation occurs when a mediating neuron decreases the repolarizing K^+ current in a presynaptic cell, prolonging the action potential, increasing the Ca^{2+} influx and NT release. In this case, presynaptic facilitation results in an enhanced response, increasing the amount of NT released by postsynaptic cell.

Postsynaptic inhibition occurs when a mediating neuron hyperpolarizes another neuron, decreasing the probability that the postsynaptic neuron will be able to generate an action potential. Postsynaptic inhibi-

tion occurs when an agonist binds to a postsynaptic $GABA_A$ receptor; these receptors are implicated in the mechanism of action of benzodiazepines and general anesthetics.

Key receptors within the CNS

General anesthetics operate by altering the ability of neurons to generate action potentials, thereby blocking elaborate paths of conscious perception within the CNS. These agents act by influencing synaptic transmission through ion channel function at either presynaptic or postsynaptic sites within the spinal cord and/or brain. Anesthetic effects on ligand-gated ion channels can either favor an open state of the channel and boost signal transmission or favor a closed state and inhibit signal transmission.[20] Thus, an anesthetic is usually an agent that in some manner enhances inhibitory communication or blocks excitatory conduction. Receptors central to anesthetic function within the CNS include inhibitory GABA and glycine receptors, excitatory NMDA receptors, background K^+ channels, and nicotinic ACh receptors.

Just as ACh receptors have subtypes (eg, nicotinic and muscarinic) that are distributed differently within the neural net, the loci of receptors affected by general anesthesia also have subtypes with specific distribution patterns. Moreover, the relative rate and/or affinity of an anesthetic for its locus of action may vary based on the patient's physiologic milieu. As a result, anesthetics with similar clinical actions may exhibit diverse side effect profiles, and these profiles may vary from patient to patient.

Major inhibitory pathways

• *GABA.* Inhibitory GABA receptors are ubiquitous within the CNS; GABA is the key inhibitory NT within the brain. At least 2 subtypes of GABA, A and B, have been well delineated.[21] $GABA_A$ receptors mediate an increase in Cl^- conductance across the postsynaptic membrane causing hyperpolarization and neuronal inhibition. While GABA is the endogenous ligand for this receptor, binding sites for benzodiazepines, barbiturates, and anesthetic steroids have been identified.[11] Volatile anesthetics and ethanol are reported to affect this receptor.[22]

$GABA_A$ receptors consist of various $\alpha_{1\text{-}6}$, $\beta_{1\text{-}4}$, $\gamma_{1\text{-}4}$, δ, ε, and/or $\rho_{1\text{-}2}$ subunits with the predominant structure comprising $2\alpha_1$, $2\beta_2$, and $1\gamma_2$ subunits.[23] The individual expression of both $GABA_A$ receptor subunit composition and subunit isoforms can modify the response to a particular anesthetic agent.

$GABA_B$ receptors are linked via G proteins to K^+ channels; when activated, $GABA_B$ receptors decrease Ca^{2+} conductance and inhibit cAMP (cyclic adenosine monophosphate) production. $GABA_B$ receptors currently have not been identified as playing a role in the mechanism of action of any anesthetic agents. The presence of $\rho_{1\text{-}3}$ subunits is considered to define the $GABA_C$ receptors.[20] Like $GABA_A$ receptors, $GABA_C$ receptors appear to act as ligand-gated Cl^- channels.

• *Glycine.* Glycine is the major inhibitory NT within the spinal cord and brainstem. The glycine receptor has 5 known subunits, $\alpha_{1\text{-}4}$ and β.[20] Glycine, along with other amino acids—alanine, taurine, serine, and proline—bind to the glycine receptor.[21,23] Volatile anesthetic and alcohol binding at glycine receptors significantly potentiates Cl^- conduction and depresses neural function.[24] Glycine-mediated, along with $GABA_A$-mediated, inhibition of Cl^- ion channels within the spinal cord could explain loss of spinally mediated reflexes under anesthesia.

Major excitatory pathways

• *NMDA.* The amino acids glutamate and aspartate are the major excitatory NTs within the CNS; binding to the glutamate receptor will increase the probability of channel opening and enhance neurotransmission by increasing primarily Na^+ and in some cases Ca^{2+} conductance.[23,25] Among the 3 classes of glutamate receptors (AMPA, NMDA, and kainite), the NMDA receptor has the most functional significance for anesthesia. All glutamate receptors are highly permeable to Na^+ and K^+, while the NMDA receptor also is highly permeable to Ca^{2+}.[20]

NMDA receptors play an extensive role within the memory and learning areas of the hippocampus and are found in large concentrations in central respiratory control centers.[26] While Mg^{2+} blocks ion flow through the NMDA receptor, there are conflicting reports regarding the efficacy of administering intravenous Mg^{2+} to elicit analgesic effects.[27] In its role as an NMDA antagonist, Mg^{2+} also appears to amplify the analgesic effects of morphine sulfate.

• *K+ channels.* Background K^+ channels form a large group of K^+ leak channels (TASK and TREK), whose activation serves to influence both resting membrane potential and the repolarization phase of the action potential. These channels, via $I_{K(An)}$, are opened by volatile anesthetics, inducing hyperpolarization and reducing the likelihood of cellular depolarization.[19] Activation of these TASK channels by volatile anesthetics hyperpolarizes the membrane and suppresses action potential generation.[28] TASK-1 K^+ channels in carotid body cells may be partly responsible for suppressing the hypoxic drive during general anesthesia.[29]

• A*cetylcholine.* Nicotinic ACh receptors are nonspecific cation channels that are typically differentiated into 2 groups: the muscle subtype found in skeletal muscle and the neuronal subtype found within the CNS and autonomic ganglia.[23] Both neuronal nicotinic and muscarinc ACh receptors are found in the brain and spinal cord. Cortical cholinergic defects are associated with disturbances in conscious awareness, hallucinations, and some degenerative brain diseases.[30] Rapid eye movement sleep, the active sleep state of dreaming, is associated with activation of the cholinergic system.

Specific subtypes of neuronal ACh receptors are inhibited by both volatile and intravenous anesthetics to a much greater degree than muscle ACh receptors.[31] Anesthesia interventions at the neuronal ACh receptors are long-standing. The muscarinic antagonist scopolamine was used to induce "twilight sleep" and memory loss. Physostigmine, a cholinesterase inhibitor that raises the concentration of ACh within the ACh synaptic cleft, is used to promote the return to consciousness after general anesthesia.[30] Ketamine also is a powerful inhibitor of neuronal nicotinic ACh receptors that contributes to its anesthetic properties.[23] Droperidol inhibits the α_7 neuronal nicotinic ACh receptor and has been implicated as the supposed target for mediating neuroleptanesthesia.[32]

• *Neuropeptides.* Opioid receptors and their endogenous ligands have been well characterized.[33] The extent and distribution of opioid receptors form the basis for spinal and supraspinal analgesia. The identified opioid receptors and their endogenous opioid peptides include μ receptors (β-endorphin, endomorphin-1 and endomorphin-2), δ receptors (metenkephalin and leuenkephalin), κ receptors (dynorphin), and ε receptors (β-endorphin).[34] Actions of exogenous agonists at these receptors include analgesia, depression of respiratory function, decreased gastrointestinal motility, and sedation, but not all of the key elements of general anesthesia. Ketamine has been shown to interact with μ receptors and contribute to both analgesia and respiratory depression.[26] The analgesic effects of nitrous oxide are due in part to the release of endogenous opioid peptides in the periaqueductal grey.[35]

• *Alpha$_2$ agonists.* Alpha$_2$-adrenergic receptors are distributed throughout the CNS and are well known for their role in depression. At least 3 subtypes of the α_2 receptor have been identified (α_{2A}, α_{2B}, and α_{2C}), though subtype selective ligands are not yet clinically available.[36] The α_{2A} receptor subtype plays a role in sedation and analgesia due to its high concentration in the locus ceruleus of the brainstem and in the spinal cord, respectively.[37] Alpha$_2$ agonists have sedative-hypnotic, analgesic, and anxiolytic actions that have a MAC-sparing effect. The analgesic effects of nitrous oxide are mediated in part by spinal α_{2B} receptors; however, this effect is sustained for only 60 minutes.[35,36]

Mechanisms of anesthetic agents

Intravenous and volatile anesthetics generally exert their effects on a variety of targets by either facilitating inhibitory transmission or blocking excitatory transmission (Table 1). Propofol, barbiturates, etomidate, and benzodiazepines are agonists at the $GABA_A$ receptor eliciting varying degrees of sedation/hypnosis, muscle relaxation, and anxiolysis.[11,24]

Ketamine, nitrous oxide, and xenon deviate from the norm and share inhibition of the excitatory NMDA receptor as a mechanism of action with essentially no effects on the GABAergic system.[38] In addition, ketamine and nitrous oxide are potent agonists at the opioid μ receptors and may reduce glutamergic excitatory transmission by presynaptic inhibition of NT release.[39] The interaction of ketamine with supraspinal μ receptors contributes to both analgesia and respiratory depression.[26] Ketamine appears to exert its sympathomimetic effects by inhibiting parasympathetic activity in the brainstem cardiac neurons via inhibition of Na^+ channels and presynaptic nACh receptors.[17] Droperidol has been demonstrated to exert biphasic effects on the $GABA_A$ receptor: at low concentrations, droperidol inhibits $GABA_A$ activation by a maximum of 25%, while at high concentrations, droperidol can activate the $GABA_A$ receptor.[32] This biphasic effect may be responsible for the anxiety and dysphoria that limit its clinical usefulness. Droperidol's mechanism of action for general anesthesia includes both GABAergic facilitation and inhibition of nicotinic ACh receptors.

Dexmedetomidine and clonidine, nonselective α_2 agonists, provide pharmacologically reversible sedation and analgesia with minimal respiratory depression.[37,40] These agents have been suggested for use as perioperative sedation, to stabilize intraoperative course under general anesthesia, as adjuncts to regional anesthesia, and for use in chronic pain syndromes.[41]

Although the enhancement of GABAergic transmission by volatile anesthetics is considered by many researchers to be the dominant factor in producing anesthesia,[13,16] recent data suggest that volatile anesthetics exert their effects on a variety of neural receptors within the brain and spinal cord including $GABA_A$, glycine, K^+ channels, and ACh receptors (see Table 1).[19,22,24,28,31,42-44] Enflurane and isoflurane have been demonstrated to directly depress glutamate currents in the hippocampus; research now suggests that

Table 1. Major anesthesia related receptors, mechanisms of action, and clinical correlates*

Membrane receptor	Endogenous effector	Location	Characteristics	Clinical application
$GABA_A$	GABA	Cerebral cortex Thalamus Reticular formation	Mediates Cl^- conductance with membrane hyperpolarization. Decreases probability of action potential firing by ↑ frequency of channel opening and/or ↑ mean channel opening time.	**Effects enhanced by:** Barbiturates Benzodiazepines Etomidate Ethanol Propofol Volatile anesthetics
Glycine	Glycine Alanine Proline Serine Taurine	Brainstem Spinal cord	Mediates Cl^- conductance with membrane hyperpolarization.	**Effects enhanced by:** Ethanol Volatile anesthetics
K^+ Channels TREK-1 TREK-2 TASK-1 TASK-2 TASK-3	ACh Glutamate H^+ Norepinephrine Serotonin Substance P	**Strongly expressed:** Spinal cord Dorsal root ganglia Corpus callosum Cerebellum Caudate nucleus/ putamen **Moderately expressed:** Cerebral cortex, hippocampus, hypothalamus, heart	Mediate K^+ influx and membrane hyperpolarization at both presynaptic and postsynaptic level.	**Effects enhanced by:** Volatile anesthetics
Opioid μ δ κ ε	Peptides β-endorphin Dynorphin Leuenkephalin Metenkephalin	Brain Spinal cord	Prevents Ca^{2+} influx into presynaptic terminal. Reduces glutaminergic excitatory transmission.	**Effects enhanced by:** Ketamine Nitrous oxide
Presynaptic α_2-adrenergic α_{2A} α_{2B} α_{2C}	Norepinephrine Epinephrine	↑ Receptor concentration in brainstem locus ceruleus and spinal cord (α_{2A})	Activation inhibits voltage dependent Ca^{2+} channels. Decreases norepinephrine release. Decreases cellular cGMP.	**Effects enhanced by:** Clonidine Dexmedetomidine Nitrous oxide
Acetylcholine nnACh nmACh	ACh	**Nicotinic subtype:** Brain Spinal cord Autonomic ganglia **Muscarinic subtype:** Cerebral cortex Cerebellum Brainstem Hippocampus	**Nicotinic:** Mediates cation influx and membrane depolarization. **Muscarinic:** G-protein linked inhibition of adenylyl cyclase, stimulation of phospholipase C, or regulation of K^+ channels.	**Effects blocked by:** Volatile anesthetics Intravenous anesthetics
NMDA	Glutamate Aspartate	Hippocampus Medullary respiratory control center	Mediates Na^+, K^+, and Ca^{2+} conductance with membrane depolarization.	**Effects blocked by:** Ketamine Nitrous oxide Xenon Extracellular Mg^{2+}

*** TREK indicates TWIK- (tandem of P domains in a weak inward rectifying K^+ channel) related K^+ channel; TASK, TWIK-related acid sensitive K^+ channel; cGMP, cyclic guanosine monophosphate; GABA, λ-aminobutyric acid; ACh, acetylcholine; NMDA, N-methyl-D-aspartate; nnACh, neuronal nicotinic acetylcholine; nmACh, neuronal muscarinic acetylcholine.**

spinal cord motor neurons also are sensitive to these currents.[45] Investigators have identified a decrease in T-type Ca^{2+} channel current in dorsal root ganglion neurons elicited by volatile anesthetics (halothane, enflurane, and isoflurane), while ventricular myocytes were insensitive to this inhibition.[46] The volatile agents halothane, enflurane, and isoflurane also inhibit the function of substance P receptors to 50% of control at approximately 2 MAC, leading to a reduction in nociceptive response.[47] Volatile anesthetics have been shown to increase the uptake of glutamate, potentially reducing its excitatory effects within the CNS and providing a neuroprotective effect.[48]

Discussion

The interaction between anesthetics and proteins have been studied on a molecular level and their characteristic interactions are beginning to become clinically relevant.[15] Research suggests that anesthetics may act on the same receptor type but with different actions within the receptor subunits. It also has been shown that altering the subunit structure of a receptor alters its ligand binding affinity.[14] Clearly, within these targets, multiple variables differentiate the actions of various anesthetic agents.

Signal transduction, the biomolecular mechanisms by which receptor activation or inactivation is signaled to the intracellular machinery, has been suggested as the elusive unitary mechanism of action. Possible targets, such as guanine nucleotide-binding protein (G protein) receptor coupling and protein kinase C activity, are downstream events that are difficult to research. One downstream unitary mechanism suggested involves a nitric oxide-cGMP (cyclic guanosine monophosphate) signal transduction system. This system is associated with second messengers involved in both excitatory NMDA and muscarinic ACh receptors and inhibitory GABA and α_2 receptors. Inhibition of nitric oxide and the associated decrease in cGMP reduces MAC of volatile anesthetics and the intravenous agents thiopental, propofol, dexmedetomidine, and ketamine.[49]

What is now becoming clear is that a wide variety of anesthetic agents have diverse actions on many key receptors within the brain and spinal cord.[14] In fact, profiles of different agents demonstrate that effective doses for different endpoints of anesthesia (hypnosis, immobility to noxious stimuli, blunting cardiovascular response to stimuli) span a significant dose range.[50] This knowledge explains clinical effects such as the fact that 10 mg of diazepam ($GABA_A$ agonist) reduces the MAC of volatile agents while 10 mg of morphine (μ agonist) does not. Knowledge of the various effects of agents on key receptors provides the opportunity to balance an anesthetic with complementary drugs.

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