

Mechanism of action of general anaesthetic drugs

Barbara J Pleuvry

Abstract

The mechanism by which drugs can cause a reversible loss of consciousness is still the subject of intense debate. An enduring finding has been that lipid solubility correlates with anaesthetic potency, indicating a lipophilic site of action. Suitable sites are the cell membrane bilayer and the proteins imbedded in it. All anaesthetics can affect voltage-gated ion channels, but in general these effects occur at greater concentrations than those necessary to produce anaesthesia. Neurotransmitter receptors, particularly the ligand-gated ion channels, are particularly sensitive to anaesthetic agents. Attention is drawn to the receptors activated by the excitatory amino acids as ketamine blocks the channel of the N-methyl-D-aspartate (NMDA) receptor. However, many anaesthetics enhance inhibitory transmission via the γ -aminobutyric acid A (GABA_A) receptor, although the binding site that mediates this effect varies for individual agents. Recent evidence suggests that some separation between the wanted and unwanted effects of anaesthetics may be possible.

Keywords GABA_A receptors; ligand-gated ion channels; membrane fluidization; NMDA receptors; voltage-gated ion channels

General anaesthesia is a loss of sensation with a loss of consciousness. The mechanisms by which drugs can produce this state are uncertain, principally because the mechanism by which the brain produces consciousness is unknown. Many of the observations described below are concerned with what anaesthetic agents do at the molecular level rather than how they cause a loss of consciousness, and there is a view, which is gaining support, that studies on anaesthesia and consciousness should be integrated.

Anaesthetic agents have many effects on the lipids and proteins that are found in neuronal membranes and most researchers believe that this is the site of their action.

The membrane consists of a phospholipid bilayer with proteins embedded in it. The proteins associated with the membrane may be associated with the internal or external surface of the membrane or embedded within the membrane. They have polar regions in contact with the aqueous media. There are four main classes of membrane proteins: enzymes, such as acetyl

cholinesterase; transporters for specific molecules; neurotransmitter receptors; and structural proteins.

The correlation of oil/gas partition coefficient with anaesthetic potency has been repeatedly confirmed for a wide range of compounds that have general anaesthetic properties, ranging from the inert gas xenon to complex steroids. Both the membrane's lipid bilayer and the integral proteins contain hydrophobic sites that could be the target of anaesthetic action.

Interactions with the membrane lipid bilayer

The lipid bilayer consists of two rows of closely packed phospholipid heads, with extended tails that exist in a gel-like state that is highly ordered and in which there is little movement. Transition from this state to a more fluid, liquid-like state can occur by a small increase in temperature or the insertion of small molecules, such as anaesthetic gases and vapours, into the bilayer. There is a positive correlation between the fluidization of phospholipid heads and anaesthetic potency. It is logical to assume that fluidization would be reversed by increases in pressure. Thus the well-established pressure reversal of anaesthesia would be consistent with fluidization of the lipid bilayer being relevant to anaesthetic action. Although changes in fluidity could cause a change in membrane function that equates with anaesthesia, most researchers have discarded this hypothesis. At anaesthetic concentrations the fluidization produced by anaesthetic agents is equivalent to that produced by a 1°C increase in temperature. Minor elevations of temperature do not cause anaesthesia, indeed cooling rather than heating increases anaesthetic potency. In addition some alcohols, which cause anaesthesia, do not seem to fluidize lipid bilayers and there is some structural dependency of some molecules with anaesthetic action that is not compatible with a simple fluidization hypothesis.

Critical volume hypothesis: an observation that anaesthetic drugs occupy space in membranes, dependent on molar concentration and volume, leads to the hypothesis that anaesthesia occurs when the molecules of an anaesthetic agent occupy a critical volume within the membrane. At anaesthetic concentrations, experiments have shown that membranes expand by a consistent 0.4%, although the anaesthetic's volume is only 0.02% of the membrane. It was proposed that such an expansion could disrupt ion channels necessary for cell functioning. The observation that anaesthesia could be reversed by increasing the ambient pressure (so that the membrane could revert to its normal size) seemed to support the premise that membrane expansion was the key to anaesthesia. However, there is evidence that pressure reversal is not the same for all anaesthetic drugs. While the greatest differences in the characteristics of pressure reversal were seen with individual intravenous agents, even the anaesthetic vapours and gases did not show a common pattern. The differences were explained in terms of a multisite expansion hypothesis, which suggests that anaesthetic agents may expand more than one site and that the physical properties of these sites vary. In addition, pressure and the anaesthetic may act on different sites (i.e. a physiological or functional antagonism). This hypothesis received much criticism on both methodological and interpretative grounds, but it did seem to free up ideas concerning possible multiple sites of anaesthetic action.

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Interactions with membrane proteins

Early studies with the enzyme luciferase demonstrated that anaesthetic gases and vapours could inhibit this enzyme in parallel with anaesthetic potency. Subsequently interactions with many types of protein have been demonstrated but have not been proved to be the definitive site of anaesthetic action.

Voltage-gated and ligand-gated ion channels are particularly sensitive to anaesthetic action. General anaesthetic drugs, like local anaesthetics, can block voltage-gated sodium channels but a diminution in axonal conduction occurs only in concentrations greater than that necessary to produce general anaesthesia. Similarly, inhalational anaesthetics can be shown to inhibit voltage-gated calcium channels and activate potassium channels. The type of channel affected varies from agent to agent and much of this work has been done *in vitro* or in the snail and so its relevance to anaesthesia in mammals is uncertain.

Ligand-gated ion channels (Table 1) are probably the most popular candidates for the site of anaesthetic action. In general the anaesthetics inhibit or block excitatory ligand-gated ion channels and enhance the sensitivity of inhibitory ion channels such as γ -aminobutyric acid A (GABA_A) receptor. Blockade of the ion channel in the N-methyl-D-aspartate (NMDA) type of glutamate receptor by ketamine aroused great interest. However, ketamine is an atypical dissociative anaesthetic that most pharmacologists could accept to be acting by a mechanism not mirrored by other anaesthetics. Nevertheless, isoflurane also decreases the probability of the NMDA channel opening and ethanol and diethyl ether have been shown to have some preferential depressant effects on NMDA receptors. Many anaesthetics, including the intravenous and inhalational agents as well as melatonin (the nocturnal hormone produced by the pineal gland) can enhance GABA transmission via the GABA_A receptor. The GABA_A receptor is a pentamer (Figure 1) usually consisting of two α , two β and one γ subunit. Each of these subunits has a number of variants giving an enormous array of GABA_A receptors with slightly different binding properties. Studies in molecular biology have shown that the presence of a particular domain, or binding site, is necessary for these potentiating effects of a given anaesthetic agent. Interestingly, the domain is not the same for all anaesthetics, indicating multiple modulatory sites on the GABA_A receptor. One research group have identified two isoforms of the GABA_A receptor that interact with etomidate (see Further Reading). The isoform containing the

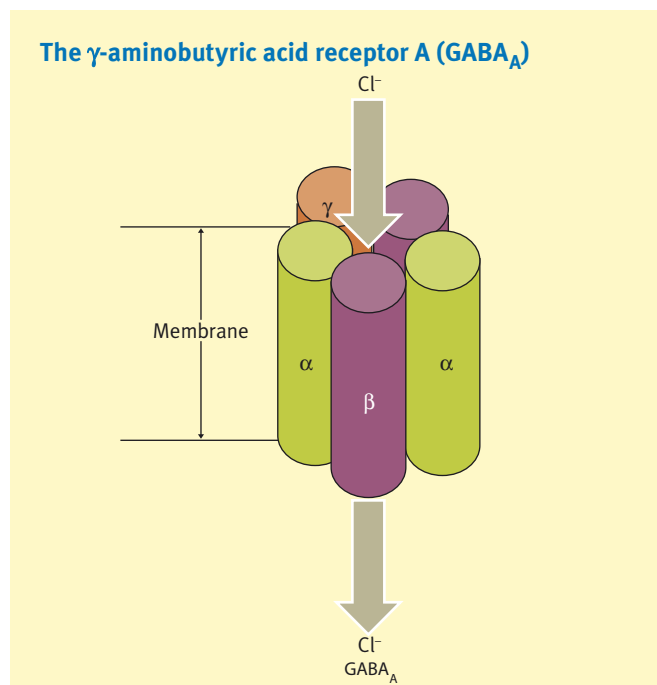


Figure 1

β_3 variant subunit seemed to mediate loss of consciousness, while isoforms containing the β_2 variant subunit mediated sedation. Indeed, mice that have a point mutation of the β_3 variant subunit are resistant to the loss of both righting reflex and paw withdrawal reflex induced by etomidate, propofol, enflurane and halothane. However, they still respond normally to alphaxalone, which binds to the neurosteroid recognition site on the GABA_A receptor.

Inhibition and/or block of excitatory neurotransmission within the CNS are tempting explanations for anaesthesia, but until the biochemical basis of consciousness is elucidated nothing can be certain. ◆

Ligand-gated ion channels sensitive to anaesthetic gases and vapours

- Nicotinic acetylcholine
- GABA_A (γ -aminobutyric acid receptor A)
- Glycine
- Glutamate receptors
 - NMDA (N-methyl-D-aspartate)
 - AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate)
 - Kainate
- 5-HT₃ (5-hydroxytryptamine 3 receptor)

Table 1

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