MECHANISMS

Mechanisms of general anaesthesia

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The term anaesthesia, components of the anaesthetic state and the importance of its integrative nature are considered in this review article. Although the lipophilicity of all anaesthetic agents suggests that membranes are important sites of action for this diverse group of agents, it does not pinpoint any particular membrane or membrane protein as crucial to anaesthesia. Anaesthetics exhibit a wide variety of molecular interactions, involving lipid bilayers and membrane proteins. The Lipophilic Invasion Protection Organization – Integrative Design (LIPOID) hypothesis of anaesthesia illustrates the possibility of many anaesthetic interactions being important in anaesthesia and suggests how chaos may be prevented despite the many simultaneous functional changes that occur following the application of anaesthetics.

If a group of 20 anaesthetists were asked to define anaesthesia, 21 different answers would be given. The term ‘anaesthesia’ must be explored before attempting to define the phenomenon of anaesthesia. It is unlikely that a single hypothesis would explain this complex phenomenon at the molecular level. However, there may be a unifying principle behind the manifold actions of anaesthetics on the organism.

What is anaesthesia?

Definition of anaesthesia

The terms anaesthesia (Greek: without feeling) and narcosis (Greek: stupor, paralyis) were coined to describe the effects of etherization. Following this, attempts were made to explain what happened during etherization, but the terms highlight two different aspects of etherization, indicating that neither is sufficient to describe the full effect. Since then, the term anaesthesia has been used with three different meanings: firstly, the clinical goal of rendering a patient fit for surgery by abolishing the sensation of pain and the reaction to pain; secondly, the anaesthetic technique of administering suitable drugs, that is anaesthetics (Figure 1), to achieve this clinical goal; and thirdly, the anaesthetic state, that is the spectrum of all clinical and functional effects of anaesthetic agents during the application of anaesthetic techniques. The term ‘anaesthesia’ may, therefore, refer to both cause and effect. This article will deal with the third meaning of anaesthesia, the anaesthetic state as defined above.

Components of the anaesthetic state

Anaesthesia is often described as a triad consisting of sleep (narcosis), muscle relaxation and analgesia. However, the Guedel scheme indicates that during anaesthesia many more functions are affected. Depending on the drug concentration, ether anaesthesia is characterized by loss of consciousness, pain sensation, memory, eyelid and corneal reflexes and muscle tone, as well as important effects on the cardiovascular, respiratory, renal and hepatic systems. Anaesthetic drugs differ in their range of effects. It is therefore highly probable that several different mechanisms are involved in producing anaesthesia. There are no complete, molecular, descriptions of the various forms of sleep, memory and pain at present. These components play an important role in the anaesthetic state and lack of knowledge of their mechanisms may explain why a comprehensive theory of anaesthesia is elusive.

Actions of anaesthetics

Meyer and Overton independently discovered that, despite the diversity of anaesthetic molecules (Figure 1), there is one unifying principle: anaesthetic potency correlates with the lipophilicity of an anaesthetic drug. This correlation holds for inhaled anaesthetics as well as for intravenous anaesthetics belonging to the class of hypnotics (Figure 2), indicating the importance of membranes as molecular sites of action.

Lipid theories vs protein theories

Most molecular theories of anaesthetic action belong to one of two categories, stressing either the lipid bilayer or membrane protein as the major site of anaesthetic action. The lipid bilayer theories assume that anaesthetics alter the properties of the lipid bilayer which affects the functions of embedded membrane proteins. In contrast, protein-based theories of anaesthetic action postulate that anaesthetics alter the functions of membrane proteins through direct interaction. The experimental evidence supporting these theories is contradictory. This contradiction may be resolved if the two different theories are not considered exclusive. The simplicity of the relationship between an agent’s lipophilicity and its anaesthetic potency led to the assumption that a simple mechanism and hypothesis existed to explain anaesthesia. However, lipophilic interactions are nonspecific. It seems likely, therefore, that anaesthetics act at
Figure 1. Drugs introduced into clinical practice differ greatly in their molecular and physicochemical properties. For the first 100 years of anaesthesia, the field was dominated by diethylether (adapted with kind permission from Ohmeda Pharmaceutical Products Division Inc, and Dr Edmond I, Eger II MD).

many different target sites, including the lipids of cell membranes and also the lipophilic domains of their membrane proteins.

**Anaesthetic actions on lipid bilayers**

Membranes adsorb and absorb anaesthetics, which can lead to changes in their properties. Lipophilic anaesthetics reside preferentially in the membrane interior, causing a thickening of lipid bilayers, an increase in membrane surface tension and a possible change in membrane fluidity. Surface-active substances, such as alcohols, are seldom found in the bilayer interior, instead adsorbing to the membrane surface where they alter the surface tension and electrical surface potential. Inhaled anaesthetics are generally less polar than alcohols; they possess properties that lie in between the two extremes. It is likely that inhaled anaesthetics would therefore be found in the membrane and at its interface. The effects of inhaled anaesthetics on lipid bilayers do not normally lead to a biologically significant bilayer electrical conductance, except at concentrations that cause membrane breakdown.

**Anaesthetic actions on membrane proteins**

A pure lipid membrane bilayer is an excellent insulator and does not permit any current or ion flow – processes which are required for the transmission of signals in biological lipid membranes. Specialized membrane proteins, called ion channels, are incorporated into lipid bilayers for this purpose. There are voltage-gated ion channels, transmitter-operated channels and channels that depend on both membrane potential and agonist activity. None of the channels permits ion flow in its resting state. Ion flow is only possible during the activation phase and, in many cases, is terminated again by an inactivated or desensitized state which differs from the resting state. Every ion channel examined so far has shown modified functional responses on exposure to anaesthetic agents.

General anaesthetics affect all three states of ion channels – resting, activated and desensitized/inactivated. Following interactions with receptor sites, a large number of specific and nonspecific effects are observed, including equilibrium shifts between the various functional states of the ion channels, changes in the kinetic properties of ion channels and their single channel conductances. Antagonistic and biphasic effects of anaesthetics are described. Membrane proteins of the same type, but originating from different tissues, can differ in their anaesthetic sensitivities. The efficacy of an anaesthetic may be modulated by membrane lipid environment. The actions of anaesthetics on several important types of ion channel, for example voltage-gated ion channels (sodium and potassium channels) and receptor-operated channels (acetylcholine or glutamate receptor channels), correlate with lipophilicity. Different anaesthetics appear to be similar in their lipophilic actions on membranes and membrane proteins, but their polar interactions may be very different.

It seems that the specificity of a lipophilic molecule is almost unimportant, or even detrimental, to producing anaesthesia. Diethylether, which dominated the first 100 years of anaesthesia (Figure 1), is a nonspecific lipophilic molecule. Isoflurane and
Figure 2. The Meyer–Overton correlation for human anaesthesia applies to inhaled anaesthetics as well as hypnotic intravenous anaesthetics. Anaesthetic potency correlates with the lipophilicity of the anaesthetic drug (slope = 1.27, r = 0.97)

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<thead>
<tr>
<th>Anaesthetic</th>
<th>IC₅₀ (M)</th>
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<tbody>
<tr>
<td>Ethanol</td>
<td>-2.5</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>-3.0</td>
</tr>
<tr>
<td>Ether</td>
<td>-3.5</td>
</tr>
<tr>
<td>Ethylene</td>
<td>-4.0</td>
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<tr>
<td>Xenon</td>
<td>-4.5</td>
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<tr>
<td>Cyclopropane</td>
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<tr>
<td>Fluorocane</td>
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<tr>
<td>Pentobarbitol</td>
<td>-6.0</td>
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<tr>
<td>Halothane</td>
<td>-6.5</td>
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<tr>
<td>Thiopental</td>
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<td>Methohexital</td>
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<td>Methoxyflurane</td>
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<tr>
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</tr>
<tr>
<td>Enflurane</td>
<td>-9.5</td>
</tr>
<tr>
<td>Propofol</td>
<td>-10.0</td>
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Log (Octanol/water partition coefficient)

IC₅₀: typical serum concentration of intravenous anaesthetic during clinical anaesthesia or equivalent aqueous concentrations of volatile anaesthetics at 1 MAC

enflurane serve as other examples: their clinical actions are almost indistinguishable, yet they hydrogen-bond differently and have different effects on in vitro preparations. Concerning detrimental effects, the partial fluorination of diethyl ether yields the clinical drug fluoroethyl (indoklon). This molecule can form several hydrogen bonds and is a convulsant agent, though at higher concentrations it still has anaesthetic properties. The polar functional groups of anaesthetic molecules seem to determine clinical side-effects, while the nonspecific lipophilic portions of the molecule are responsible for general anaesthetic action.

Integrative nature of the anaesthetic state

Action on the CNS

The adequacy of anaesthesia, defined as fitness for surgery, is not an absolute quantity but is influenced by factors other than the dose and concentration of anaesthetic agent; for example, the intensity of the pain stimulus.

While it is essential to understand anaesthetic actions at the molecular level, a complete picture of the mechanisms of anaesthetic actions is not possible without considering their integration at all levels of the central nervous system (CNS), starting at the molecular level and ending with the intact brain. As each level of the CNS constitutes more than the sum of its individual components, it is important to consider how the components are connected together. Even small anaesthetic effects, on components at one level of CNS integration, can have substantial consequences when these components are integrated into a new functional unit.

LIPOID hypothesis of anaesthesia

The view that anaesthesia results from specific interactions of anaesthetics with some key membrane proteins is popular, but does not take into account the fact that anaesthetics show a bewildering variety of different interactions at all levels of the CNS. If many of these interactions at the molecular level occurring at clinically relevant concentrations are irrelevant to the production of the anaesthetic state, how are the effects resulting from these interactions compensated for and prevented from reaching higher levels of integration within the CNS? How is it possible that, during general anaesthesia, the various physiological reflexes and responses of a patient are turned off in an orderly, dose-related fashion without causing chaos or death? The clue may be found in the lipophilicity of anaesthetic actions. Lipid membranes play a key role in living organisms, allowing the separation and differentiation of various processes vital to life. The lipid bilayer is instrumental in providing a selective barrier for import into, and export from, a cell or a subcellular organelle. This works very well for ions, polar substances and electrical signals, but lipophilic substances can easily overcome this barrier, thereby possibly disrupting membrane function as well as other protein functions within the cell. Lipophilic substances as exemplified by inhaled anaesthetics pose a substantial threat to any organism. They are dangerous substances as their therapeutic index is very narrow and overdosing can easily lead to death.

One may postulate that early in evolution, organisms must have developed defence mechanisms against the lipophilic threat from without and from within. Graded and tuned responses, related to the severity of the lipophilic threat, may have developed at various levels of the CNS, switching off non-essential life processes while maintaining those needed for survival.

Our LIPOID (Lipophilic Invasion Protection Organization – Integrative Design) hypothesis of anaesthesia postulates that organisms have developed different, hierarchically organized and integrated, defence mechanisms against the invasion of lipophilic substances. Depending on its molecular structure and specificity, an anaesthetic molecule may trigger some or many of these defence mechanisms, leading to anaesthesia. The LIPOID hypothesis is speculative at this point, but its purpose is to illustrate the possibility of many anaesthetic interactions being relevant to anaesthesia.

References


