1

Concepts and Mechanisms of General Anaesthesia

LEARNING OBJECTIVES

- To be able to define general anaesthesia.
- To be able to discuss general anaesthesia in terms of its component parts, i.e. the triad of general anaesthesia.
- To be able to define balanced anaesthesia.

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1.1 Definitions

Anaesthesia literally means 'lack of sensation/feeling' (from *an* meaning 'without' and *aesthesia* pertaining to 'feeling'). Therefore, general anaesthesia means global (total) lack of sensations, whereas local (or regional) anaesthesia relates to lack of sensation in a localised (or regional) part of the body.

General anaesthesia can be defined as a state of unconsciousness produced by a process of controlled, reversible, intoxication of the central nervous system (CNS), whereby the patient neither perceives nor recalls noxious (or other) stimuli.

General anaesthesia is, however, often referred to as the state of the patient when the three criteria in the triad of general anaesthesia have been met.

1.1.1 The Triad of General Anaesthesia

1) **Unconsciousness:** no perception or memory (therefore including **amnesia**) of any sensory, or indeed motor, event.
2) **Analgesia** (or, more correctly in an unconscious patient, **antinociception**): can also be thought of as suppressed responses/reflexes to nociceptive sensory inputs.
3) **Suppressed reflexes:** autonomic (e.g. haemodynamic, respiratory and thermoregulatory) and somatic (e.g. proprioceptive reflexes such as the righting reflex).
   - Suppression of somatic reflexes can be useful, e.g. it can provide a degree of **muscular weakness/relaxation**.
   - Suppression of autonomic reflexes can be a nuisance (see Chapter 18 on monitoring), but **autonomic stability** can be a desirable component of anaesthesia and is often listed as a fourth component.

All these components could potentially be achieved in a patient following administration of a single 'anaesthetic' drug. If that drug, however, did not have very good, let us conjecture, analgesic properties, then large doses would be required to produce sufficiently 'deep' unconsciousness to reduce the response to noxious stimuli. Such deep anaesthesia is often associated with extreme depression of the CNS and homeostatic reflexes (Table 1.1).

An alternative approach, therefore, would be to produce each component (of the 'triad') separately by administering several drugs, each of which targets one component more specifically. This latter approach is theoretically advantageous because, by 'titrating to specific effect', relatively smaller doses of each individual drug tend to be sufficient, thereby minimising both each individual drug's, and the overall, side effects. This 'polypharmacy' approach is often referred to as **balanced anaesthesia**.

1.1.2 Balanced Anaesthesia

This is the administration of a number of different drugs, each with different actions, given during the immediate peri-operative period, to produce an overall state of general anaesthesia, which fulfils the criteria of unconsciousness, analgesia and muscle relaxation.

Table 1.1 Summary of effects of general anaesthesia.

Central Nervous System Depression
- Loss of consciousness
- Damping of reflexes
  - Cardiovascular → Hypotension
  - Respiratory → Hypoventilation
  - Thermoregulatory → Hypothermia
  - Postural → Reduced muscle tone
- Central modulation of nociception (hopefully providing analgesia/antinociception)

Cardiovascular System Depression (→ Hypotension)
- Reflex (e.g. baroreflex) suppression (centrally and peripherally)
- Changes in autonomic balance
- Changes in vasomotor tone (drug effects, centrally and peripherally)
- Myocardial depression
  - Direct (drugs)
  - Indirect (e.g. hypoxaemia, hypercapnia [acidosis])

Respiratory System Depression (→ Hypoventilation; resulting in hypercapnia/hypoxaemia)
- Reflex suppression (↓ventilatory response to ↑PCO_2 [↓pH] and ↓PO_2)
- Reduced respiratory muscle activity (incl. ↓ sighing and yawning)
- Alveolar collapse/small airway closure (atelectasis)
- Reduced functional residual capacity
- Ventilation/perfusion mismatch

1.1.2.1 Components of Immediate Peri-operative Period

- **Pre-operative assessment:** patient stabilisation; provision of (pre-emptive) analgesia.
- **Premedication:** anxiolysis/sedation and initiation/continuation of analgesia provision if not already provided.
- **Induction** of anaesthesia.
- **Maintenance** of anaesthesia; provision of muscle relaxation; continuation of analgesia/antinociception provision.
- **Recovery** from anaesthesia (sometimes referred to as 'reanimation'): aftercare; continuation of ('preventive') analgesia provision.

Prior, and subsequent, to this immediate peri-operative period, more attention is beginning to be paid to longer-term, and more holistic, strategies of patient care, in order to improve outcomes: **prehabilitation** and **rehabilitation**, respectively. These include elements of nutrition and physical therapies to optimise musculoskeletal condition, but are outwith the scope of this book.

1.2 The Depth of General Anaesthesia

Some texts refer to various stages and planes of anaesthesia that try to mark the progression of the continuum between consciousness and death. When ether was used as the sole anaesthetic agent, five 'degrees' of progression through ever 'deeper' stages of anaesthesia in people, from consciousness to deep coma, were described by John Snow; Overton did similar for chloroform. Guedel developed Snow's ideas further and, in 1937, produced a chart outlining the patient's responses at each of four successive stages of diethyl ether anaesthesia. This was developed still further by Artusio in 1954, who divided Guedel's stage 1 into three planes.

Table 1.2, included purely for historical interest, describes the features of diethyl ether anaesthesia in the dog, after Guedel. The features of these stages and planes, however, do not necessarily apply similarly to other inhalant agents, and apply even less to injectable agents, to say nothing of the combination of inhalational and injectable agents that can be administered when balanced anaesthesia is practised. Furthermore, the chart is not necessarily transferrable to other species.

For any species, although usually without ether nowadays, when balanced anaesthesia is practised to achieve the desired state/depth of general anaesthesia, and when we add surgical stimulation to the anaesthetised patient (because depth of anaesthesia is not only related to the 'dose' of drug/s administered, but is also dependent upon the degree of stimulation [usually surgery] at the time), it is important to monitor the patient's physiological responses to, and status during, anaesthesia, which are considered in more detail in Chapter 18.

Although Table 1.2 is included purely for interest, it is important to note that during induction of anaesthesia, stage II (involuntary excitement/movement) may be witnessed; and during recovery from anaesthesia, the stages tend to be traversed in the reverse order, such that emergence excitement/delirium (stage II) may be observed.

1.3 Mechanisms of Action of General Anaesthetic Drugs

Compounds that exert general anaesthetic effects exhibit a wide diversity of chemical structures and can be administered by injection (usually intravenously) or by inhalation. Although a unifying target for their action has been sought, the diversity in their structure makes a single target site unlikely.

Nevertheless, Meyer (1899) and Overton (1901), independently, reported that anaesthetic potency was strongly correlated with lipid solubility which sparked interest in lipid membranes as the site of action. It was variously hypothesised that anaesthetic agents may exert a non-selective physical perturbation of a lipid site within the membrane or possibly perturb the volume or fluidity of the membrane itself. That physical dissolution of lipid-soluble agents

Table 1.2 Stages of ether anaesthesia in the dog, after Guedel.

Stage of anaesthesia	Depression of CNS	MM colour	Pupil size	Eyeball activity	Breathing
Stage I: stage of voluntary movement/excitement	?Sensory cortex	N/flushed	Small	Voluntary	Rapid/irregular
Stage II: stage of involuntary movement/excitement 'delirium'	Motor cortex Decerebrate rigidity	Flushed	Dilated	Increased	Irregular
Stage III (light surgical): plane 1	Midbrain	Flushed/N	Smaller	Increased	Slow/regular
Stage III (moderate surgical): plane 2	Spinal cord	N	Miotic	Fixed, ventral rotation	Slow/regular
Stage III (deep surgical): plane 3	Spinal cord	N/pale	Miotic	Ventral rotation	Large abdominal component
Stage III (excessive surgical): plane 4	Spinal cord	Pale	Bigger		Abdominal/ shallow
Stage IV: paralysis (death follows respiratory and subsequent cardiac arrest)	Medulla	Pale/ cyanotic	Mydriatic	Central	None/agonal gasps

Stage	Pulse rate & BP	Palpebral reflex	Corneal reflex	Swallowing	Cough	Pedal withdrawal	Comments
I	Rapid/high	+	+	+	+	+	Analgesia?
II	Rapid/high	+	+	+	+	+	Unconscious
III (plane 1)	N/N	Poss slight	+	–	+	+	Some lacrimation persists
III (plane 2)	N/N	–	Slight	–	–	–	
III (plane 3)	Rapid/low	–	–	–	–	–	
III (plane 4)	Rapid (or slow)/ low	–	–	–	–	–	Anal reflex poor
IV	'Shocky'	–	–	–	–	–	Anal/bladder sphincters relax

MM = mucous membranes. N = normal.
Changes tabled above refer specifically to those observed during ether anaesthesia in the dog.
Surgical stimulation may alter haemodynamic and respiratory variables via autonomic reflexes which persist into stage III, planes 2–3.

within plasma membranes caused their expansion, sparked the 'critical volume' and 'membrane expansion' hypotheses, with some demonstration of pressure reversal. The **lipid theory**, however, had several problems, including the fact that some isomers with identical lipid solubilities had different anaesthetic potencies, not all anaesthetic effects were reversible with applied pressure, and small temperature changes could also change membrane volume but without anaesthetic effects.

Although microtubule and even bubble theories have also been proposed, the biggest step forwards came with the discovery, by Franks and Lieb (1984), that anaesthetic agent potency correlated with inhibition of firefly luciferase, a large globular protein. This **protein theory** was a turning point for research and focused attention on proteins as potential targets for anaesthetic agents, in particular membrane receptors and ion channels that control ionic permeabilities. That said, some anaesthetic agents appear to be able to disrupt **lipid rafts** (subsets of ordered lipids within plasma membranes), resulting in indirect activation of ion channels. For example, anaesthetic agents, through lipid raft disruption, may activate phospholipase D2 (which converts phosphatidyl choline into phosphatidic acid), and then phosphatidic acid (an anionic lipid), finally activates a two-pore-domain potassium channel, e.g. TREK-1 (see below).

Accepting that anaesthesia results from reversible CNS depression, it is plausible that either enhancement of inhibitory neurotransmission and/or inhibition of excitatory neurotransmission could produce a state of unconsciousness. Anaesthetics have therefore been proposed to act by modulation of such neurotransmission.

The main inhibitory neurotransmitter in the brain is gamma-aminobutyric acid (GABA), and the main excitatory neurotransmitter is **glutamate**. Between them, these neurotransmitters act at several key synaptic, ligand-gated ion channels: GABA at $GABA_A$ receptors; and glutamate at *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors. (Although primarily ligand-gated, the NMDA receptor requires glycine as a co-agonist and also displays a voltage-dependent magnesium block.) The majority of anaesthetic agents have been shown to interact with at least one of these targets.

Barbiturates, benzodiazepines, neuroactive steroids, propofol, etomidate and, to a lesser extent, the volatile agents, have been shown to be **positive allosteric modulators of the $GABA_A$ receptor**; that is, they produce little direct effect alone at clinical doses but instead they enhance GABA-mediated chloride currents in post-synaptic membranes. (At higher doses, however, barbiturates, propofol, alfaxalone and etomidate can act as direct $GABA_A$ receptor agonists). This produces membrane hyperpolarisation with consequent reduction in neuronal activity, resulting in depressant effects. The different anaesthetic agents, however, appear to have different preferred sites of allosteric modulation within the receptor complex. Furthermore, variations in both receptor structure (many different isoforms exist) and distribution (not only throughout the CNS but also between pre-, extra- and post-synaptic sites) increase the possibilities for differential effects.

Ketamine, nitrous oxide and xenon, and to a much lesser extent the volatile anaesthetic agents, are **NMDA receptor antagonists**, again having different sites of action within the receptor complex (e.g. isoflurane competes with glycine for its binding site, whereas xenon shows competitive and non-competitive glycine-binding inhibition). These anaesthetic agents reduce the activation/permeability of NMDA receptors to calcium and sodium, thus reducing excitation of the neuron, resulting in overall depression. NMDA receptors are also involved in the development of nociceptive- and memory-processing; hence, NMDA receptor antagonists produce analgesic, antihyperalgesic, antiallodynic and other effects.

More recently, the volatile anaesthetic agents, xenon, and to some extent nitrous oxide and even propofol, have also been shown to activate a family of so-called tandem-pore-domain or **two-pore-domain potassium (K_{2P}) channels**, especially members of the TREK subfamily, which are widely expressed in the brain and have roles in the regulation of sleep and membrane excitability more generally. Local anaesthetic agents also have actions at these channels.

Finally, many anaesthetics have also been shown to affect other, unrelated, receptors, resulting in a multitude of possible side effects: these are often undesirable but may, on occasion, be beneficial. Some of these **other sites of action** include glycine receptors, other glutamate receptors, cholinergic receptors, potassium channels (e.g. voltage-gated potassium channels and non-voltage-gated ATP-sensitive potassium channels [K_{ATP} channels]), voltage-gated calcium channels, voltage-gated sodium channels and others (e.g. hyperpolarisation-activated cyclic nucleotide-gated non-selective cation channels such as neuronal HCN1).

From this multiplicity of sites of action, we can begin to see how 'balanced anaesthesia' developed; that is, the administration of several different anaesthetic and adjunctive agents, each with a slightly different site/mode of action (or spectrum of activities), to produce an overall state of what we refer to as 'general anaesthesia', with, hopefully, fewer overall side effects because usually a lower dose of each agent suffices. Research continues into the possible similarities between natural sleep, particularly non-REM sleep, and the state of unresponsiveness during sedation and light general anaesthesia.

No matter which drug/s we use to produce general anaesthesia, our main objective is to maintain tissue perfusion, with delivery of oxygen and removal of waste products. If this fails, we can expect increased patient morbidity and mortality. There are no safe anaesthetics; there are only safe anaesthetists.

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Self-test Section

1 What are the three main types of ion channels thought to be involved in the mechanism of general anaesthesia?

2 True or False? Glycine is a co-agonist of the NMDA receptor.