Components of general anaesthesia

The clinical state of 'general anaesthesia' has various components. While immobility, stability of the autonomous nervous system, and anti-nociception are essential components, the most obvious characteristics of general anaesthesia are that the patient is unconscious and has no recall after the procedure.

The absence of recall after surgery alone does not guarantee that the patient had been unconscious during surgery. Sub-anaesthetic concentrations of anaesthetic drugs induce amnesia. These effects may not reflect an increasing global suppression of neuronal activity, but differential effects on brain areas required for memory and consciousness. Therefore, drug-induced amnesia has been characterized as a separate phenomenon from sedation. Analyzing evoked potentials, Veselis et al found electrophysiologic evidence that these phenomena should be separated from each other [1]. In an fMRI study, Kerssens et al administered increasing concentrations of sevoflurane in six volunteers. At 0%, 1% and 2% of sevoflurane, a list of 15 words was presented and 1.5 h after recovery, recall of the presented words was tested. Using fMRI, presentation of the word lists showed a characteristic activation of brain areas at 0% and 1%, while recall was only demonstrated for words presented at 0%. This indicates that auditory stimuli are processed at anaesthetic concentrations which otherwise prevent recall. In addition, explicit memory or recall represents only the tip of the iceberg. Memory of intra-operative events may not always be explicit. Patients may also have implicit (or unconscious) memory from periods of intra-operative perception or consciousness.

The main targets for the amnesic effects of the brain are the entorhinal cortex, amygdala, and hippocampus, and all of these areas are suppressed by anaesthetics. As long as amnesic effects cannot reliably be quantified, general anaesthesia should be focussed on unconsciousness rather than amnesia.

Molecular mechanisms of anaesthesia-induced unconsciousness

Ion channels

Anaesthetics affect numerous ion channels. Two pore potassium channels (K2P channels) determine the resting membrane potential which is approximately -70 mV. Open K2P channels allow potassium ions to leave the intracellular space. Entirely open K2P channels lead to a potassium equilibrium with a resting membrane potential of -90 mV. In isolated neurons, it has been demonstrated that volatile anaesthetics open K2P channels. This leads to hyperpolarisation of neurons. As studies in knock-out mice demonstrate, animals without one of the main K2P channels could not be anaesthetized with volatile anaesthetics, while intravenous agents still showed an effect. This identified K2P channels as one of the main targets of volatile anaesthetics. This effect may explain the decreased excitability of neurons, but not the blockade of excitation. In addition, the wide distribution of K2P channels in the CNS including pre- and postsynaptic sites allows only limited conclusions about the effect on the brain as a whole [2].
Neurotransmitters

Glutamate is the most important excitatory neurotransmitter in the mammalian brain. Approximately 40% of cortical synapses are glutamatergic. Excitation is also induced by acetylcholine (nicotinergic and muscarinergic). The inhibitory transmitters are gamma-aminobutyrate (GABA) and glycine. 50% of cortical synapses are GABAergic.

NMDA receptors

Glutamate produces its inhibitory effects via glutamate receptors. Glutamate activates NMDA, kainate, and AMPA receptors, which are fast ion channels. Opening of NMDA channels depends on binding of the ligand (glutamate) and on voltage. This requires binding of the co-agonist glycine.

Opening of the NMDA receptor allows passage of both sodium and calcium. While sodium leads to depolarisation, calcium is mainly responsible for long-term potentiation (LTP) and long-term depression (LTD).

In contrast to AMPA and kainate, NMDA receptors are blocked by clinical concentrations of anaesthetics. Ketamine, nitrous oxide, and xenon have their anaesthetic effects via NMDA receptors.

GABA\(_{\text{A}}\) receptors

In general, CNS activity is not reduced just by inhibition of excitatory effects, but also by enhancement of inhibitory effects. GABA\(_{\text{A}}\) leads to hyperpolarisation of neurons via chloride influx. The GABA\(_{\text{A}}\) receptor has numerous subtypes (the GABA\(_{\text{A}}\) receptor family). GABA\(_{\text{A}}\) receptors are important targets for benzodiazepines, propofol, barbiturates, and volatile anaesthetics [3]. However, there are differential effects of these drugs because they affect different subunits of the GABA\(_{\text{A}}\) receptor, and the different subunits are differentially distributed in the brain.

Other receptors

The effects of anaesthetics on numerous ion channels have been studied. HCN-type potassium channels play an important role in thalamocortical oscillations and are influenced by propofol.

Nicotinic acetylcholine receptors play an important role in activation of neuronal pathways which lead to cortical excitation. Inhibition of these receptors has been described with intravenous (propofol, ketamine) and volatile anaesthetics. In animals, thalamic injection of nicotine leads to reversal of sevoflurane-induced unconsciousness [4].

Glycine-A receptors are widely distributed in the spinal cord and explain enhancement of inhibition by anaesthetics at this level.

In addition to the described mechanisms, presynaptic effects of anaesthetics may modulate release of neurotransmitters. Inhibition of acetylcholine and glutamate release has been demonstrated for volatile anaesthetics and propofol.

While these mechanisms describe the effects of anaesthetics on the cellular level, they explain only an overall suppression of neuronal activity. In order to understand anaesthesia-induced unconsciousness, the mechanisms of anaesthesia on brain structures must be taken into account.

Anaesthesia-induced unconsciousness and targets in the brain

General anaesthesia leads to a reduction in brain glucose metabolism [5]. Together with the effects of anaesthetics on the neuronal level, this suggests a general blockade of neuronal activity. However, drug-induced unconsciousness cannot be explained by a general depression of neuronal activity. Anaesthetics induce unconsciousness not only by effects on specific molecular structures, but also by effects on specific areas of the brain.
Analysis of spontaneous and evoked electrical activity and imaging techniques allows studies in humans. This approach provides an insight into the complex interaction of different brain structures, which are required for consciousness, perception and memory. While some study results favour subcortical structures as the main target for anaesthesia, others have identified cortical effects as the underlying site of anaesthesia-induced unconsciousness.

Thalamic blockade

The thalamus has been described as the ‘gate to consciousness’. It plays an important role during perception of external stimuli. Patients with destruction of thalamic structures have intact autonomic regulation, but do not regain consciousness (‘vegetative state’). This suggests that thalamic function may be crucial for consciousness and suggest a ‘thalamocortical switch’ as the mechanism for unconsciousness. In experimental settings, thalamic deactivation by local administration of GABA or volatile anaesthetics has been demonstrated to induce unconsciousness. Animals under sevoflurane anaesthesia regain consciousness after subthalamic injection of nicotine [4].

In humans, Alkire demonstrated that anaesthesia induces hyperpolarisation of thalamic neurons, which results in reduced activity of the thalamus and reticular formation. This supports the theory of a thalamocortical switch as the mechanism of anaesthesia-induced unconsciousness [6].

On the other hand, general anaesthesia does not entirely block signal transmission through the thalamus to the cortex. This is well known from electrophysiological monitoring. For example, cortical components of auditory evoked potentials can be measured during unconsciousness and anaesthesia. Cortical signal components are altered by anaesthesia, but can still be detected. This is in contrast to the hypothesis that anaesthetic-induced unconsciousness is induced by blockade of the thalamic gate.

Cortical blockade

A different target for general anaesthesia is the cerebral cortex. The electrical activity of neocortical cell cultures is suppressed by clinical concentrations of anaesthetics. In neocortical cell cultures, cortical cells are separated from underlying subcortical structures. The fact that MACawake concentrations of anaesthetics block activity in these cell cultures supports the leading role of cortical blockade as the mechanism of anaesthesia-induced unconsciousness. In patients with intracerebral pacemaker electrodes, analysis of electrical activity showed that anaesthesia-induced ‘slowing’ of activity starts in the cerebral cortex before thalamus activity decreases [7]. Brain reactions to cortical stimulation also revealed differences between sleeping and awake subjects. Cortical responses to transcranial magnetic stimulation showed a reaction at the stimulus site with subsequent activation of different cortical areas in awake subjects. In sleeping subjects, the primary response was observed, but subsequent reactions in other brain areas did not follow [8]. This supports the view that cortical disintegration is an electrophysiological sign of unconsciousness and anaesthesia; however, it may be that cortical disintegration itself leads to unconsciousness and anaesthesia. This resembles the theory that anaesthesia induces loss of ‘information capacity’. In the awake brain, irregular, ‘chaotic’ activity allows more complex reactions to information and stimuli. In the anaesthetised subject, potentials become more regular and uniform. This may reflect a reduced capacity to process multiple and complex information. This loss of integration capacity is reflected by loss of connectivity (the interaction between cortical fields).

Anaesthesia-induced unconsciousness - multiple mechanisms at multiple sites

Anaesthetic effects at different sites of the brain do not necessarily contradict each other. The observed reduction of thalamic activity does not necessarily reflect a primary role of the thalamus. The thalamus is activated (or not) by ascending (ARAS) and descending (corticofugal, that is, corticothalamic) pathways. On one hand, this means that anaesthetic depression of cortical activity may reduce corticothalamic activity and thus reduce thalamic activity. Via this pathway, the deactivated cortex may reduce its own input. On the other hand, the thalamus and cortex can be activated by ascending input. This can reverse anaesthesia-induced unconsciousness. In an experimental setting, subthalamic injection of nicotine mimics such an activation and reverses anaesthesia-induced unconsciousness [4].
Conscious processing of signal input requires a complex integration of several components. Sensory inputs are transmitted (by the reticular formation and ventral tegmentum) to the thalamus. Specific ventrobasal nuclei project to cortical layer V, whereas unspecific intralaminar nuclei project to cortical layer I. Cortical pyramidal cells integrate information from layers I and V. Corticothalamic loops feed backward information to the thalamus. Anaesthesia affects multiple steps of this pathway. While anaesthesia-induced unconsciousness reflects mainly cortical disintegration of information, inhibition of thalamic throughput prevents arousal [9].

**Key learning points**

- On the molecular level, anaesthetics may induce unconsciousness by affecting ion channels (K2P), blockade of excitatory (glutamate, acetylcholine), or enhancement of inhibitory (GABA), neurotransmitter effects.
- The thalamus has been described as the ‘gate to consciousness’ and may be one of the main targets of anaesthesia.
- On the other hand, anaesthetics may induce unconsciousness by cortical disintegration.
- In the anaesthetised brain, potentials become more regular and less ‘chaotic’. This may reflect reduced information capacity and loss of connectivity.
- Consciousness requires integration of both thalamic and cortical functions. Anaesthetic effects which prevent thalamocortical or corticothalamic feedback may induce unconsciousness.
- While unconsciousness seems mainly induced by cortical disintegration, thalamic effects of anaesthetics are important to prevent arousal.

**References**