UCL School of Pharmacy

General anaesthetics 2025

General anaesthetics

General anaesthetics are a diverse group of compounds used during major surgery to produce a state of reversible unconsciousness for a controlled amount of time, with inhibition of sensory, motor and autonomic reflexes, loss of skeletal muscle tone, analgesia - loss of pain, touch, cold and other sensations, and amnesia.

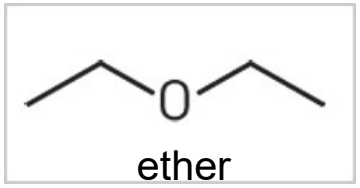
History of general anaesthesia

History of general anaesthesia

Original architecture of the old operating theatre of St. Thomas's Hospital (London) of 1822. Before the advent of general anaesthesia, an operation had to be swift. Without hand-washing or antiseptics, the chance of later infection was very high.

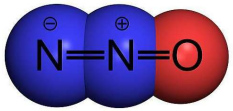
History of general anaesthesia

- The first agent used as a general anaesthetic for major surgery was **diethyl ether** in 1846, by William Morton.

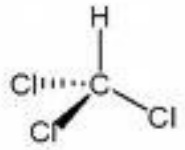


ether

- **Chloroform** was first used in 1847 and **N_2O** in 1867.

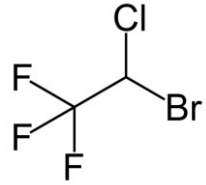



Nitrous oxide



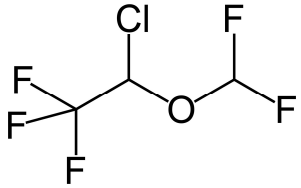
chloroform

- The first 'safe' inhalational anaesthetic was **halothane**, introduced in 1956.



halothane

- **Enflurane, isoflurane, sevoflurane** were introduced between 1972 and 1995.



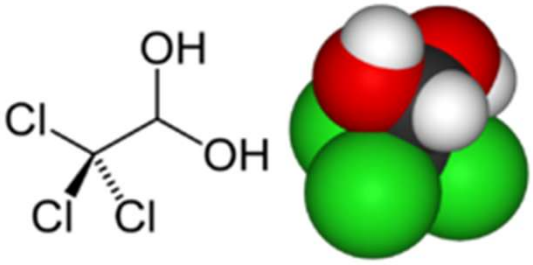
isoflurane

History of general anaesthesia

The first successful public demonstration of general anaesthesia using ether, was carried out by William T.G. Morton in Massachusetts USA in 1846. Following that demonstration, the use of ether anaesthesia became popular around the world.

History of general anaesthesia

- **Chloral hydrate** was first discovered in 1832 and its sedative/hypnotic properties recognised in 1869. It was then widely used recreationally in the late 19th century and achieved some notoriety as a "*knockout drop*" mixed with alcohol to render people incapable/unconscious for illicit purposes (to give someone a "Mickey Finn"). Its short-term use as a hypnotic now (*e.g.* in children) is very limited. Acts by potentiating $GABA_A$ effects in the brain.



Chloral hydrate

General anaesthetics

There are two types of general anaesthetics - *inhalational* and *intravenous*:

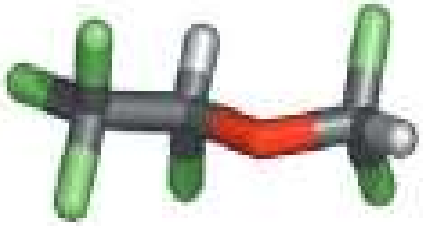
Inhalational agents: exist either as gases or volatile liquids that are vaporized and delivered to the patient with oxygen and air, via an anaesthetic machine*; e.g.* **N_2O** ('laughing' gas) or simple halogenated volatile compunds: **halothane, isoflurane, desflurane, sevoflurane.**

General anaesthetics

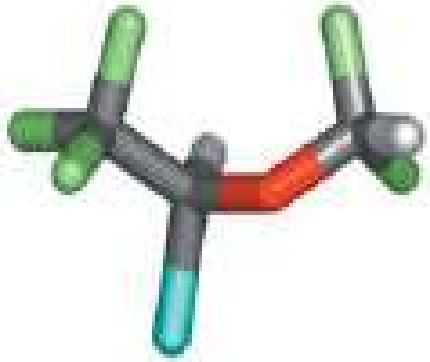
Inhalational

Nitrous oxide
N_2O

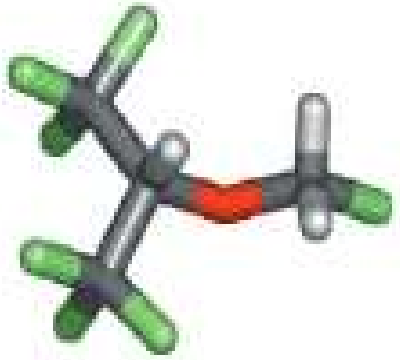
Halothane
$CF_3CHClBr$



Desflurane
$CF_3CHFOCHF_2$



Isoflurane
$CF_3CHClOCHF_2$



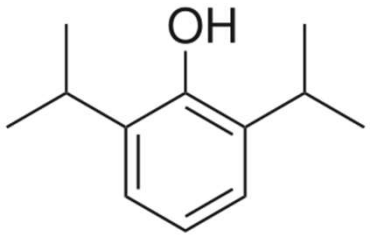
Sevoflurane
$CH(CF_3)_2OCH_2F$

General anaesthetics

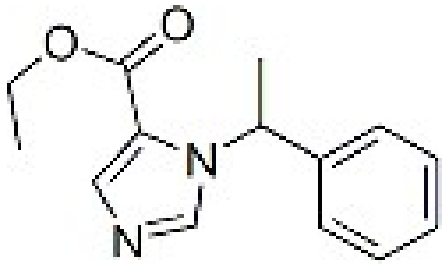
Intravenous

Intravenous agents: these are various anaesthetic compounds or induction agents given by i/v injection usually with inhaled anaesthetics to supplement general anaesthesia, or for pre-anaesthetic sedation:

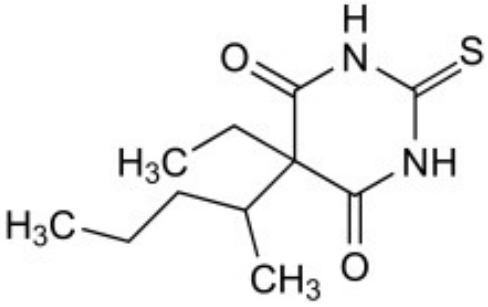
e.g. **propofol; etomidate; thiopentone, diazepam.**



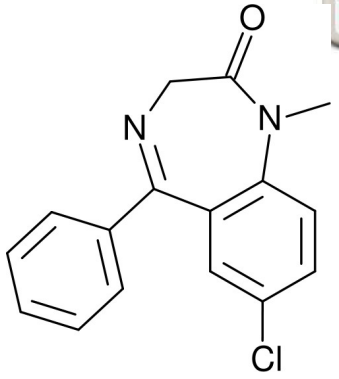
Propofol



Etomidate

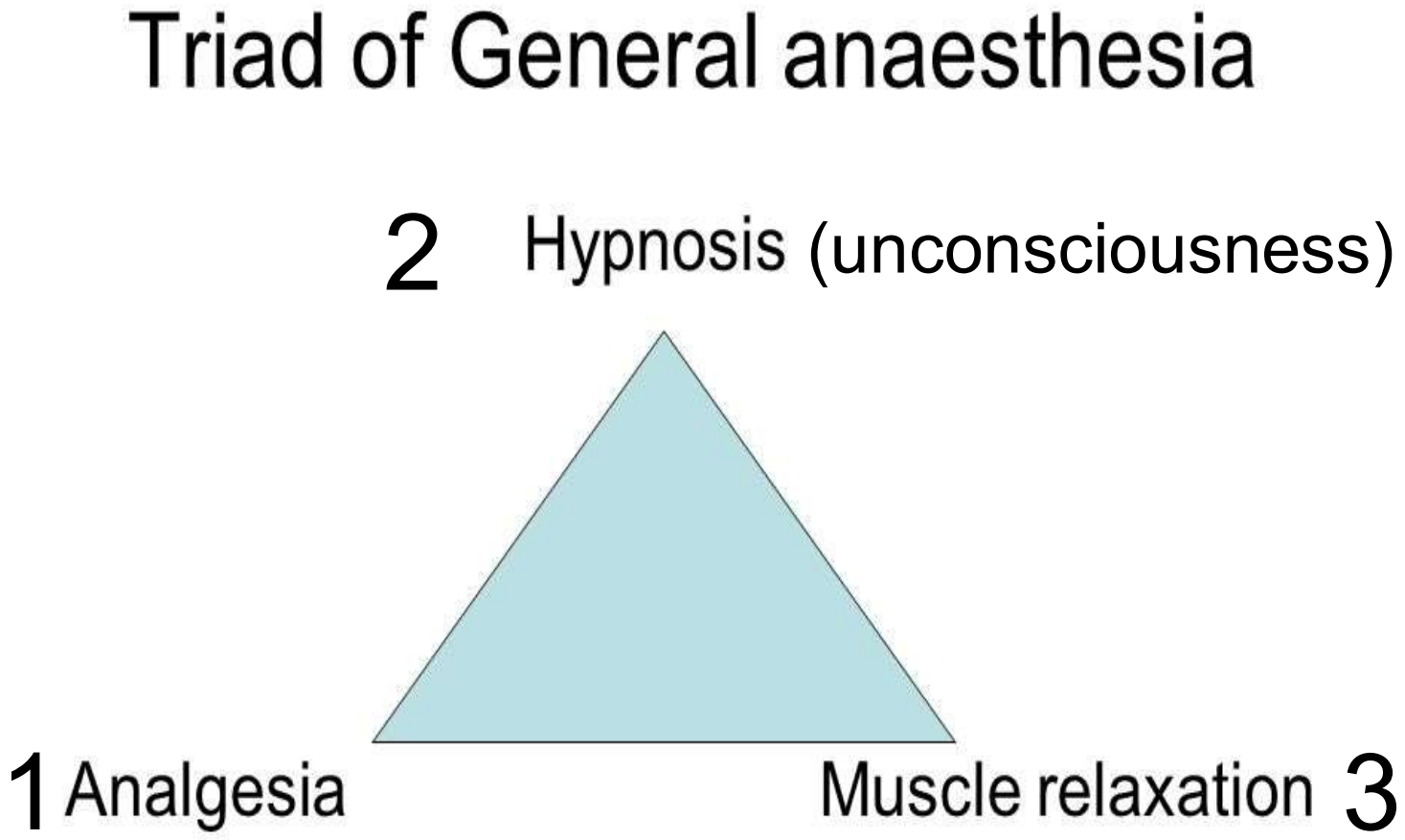


Thiopentone



Diazepam

Aims of general anaesthesia



The triad of anaesthesia is analgesia, anaesthesia and muscle relaxation. Rather than using a large dose of a single agent to achieve the anaesthetic triad, smaller, safer doses of multiple drugs, each with specific actions are used.

Stages of general anaesthesia

There are 4 classically recognized stages of general anaesthesia:

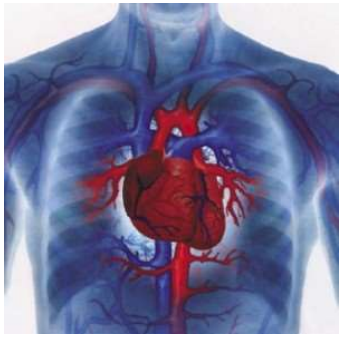
1. **Stage of analgesia: the 'induction' period;** no pain felt, respiration irregular, no amnesia.

2. **Stage of excitement: - patient is excited,** delirious, respiration and heart rate are irregular and fast, pupils dilated, possible vomiting; (period needs to be as short as possible); amnesia.

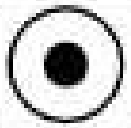
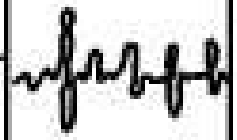
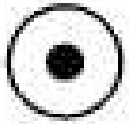
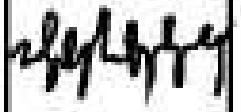
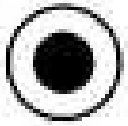
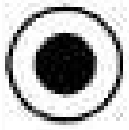
Stages of general anaesthesia

3. **Surgical anesthesia:** **operative stage** - respiration regular; loss of eyelash reflex; skeletal muscles relaxed; no eye movements; dilated pupils; surgery can begin.

4. **Medullary depression:** **danger point** - overdose - respiration ceases; cardiovascular collapse - artificial respiration and cardiovascular support required.



Stages of general anaesthesia

STAGE	PUPIL		RESP	PULSE	B.P.
	USUAL SIZE	REACTION TO LIGHT			
1ST INDUCTION				IRREGULAR	NORMAL
2ND EXCITEMENT	 OR			IRREGULAR AND FAST	HIGH
3RD OPERATIVE				STEADY SLOW	NORMAL
4TH DANGER				WEAK AND THREADY	LOW

Mechanism of action

The mechanism of action of general anaesthetics has always been a subject of debate.

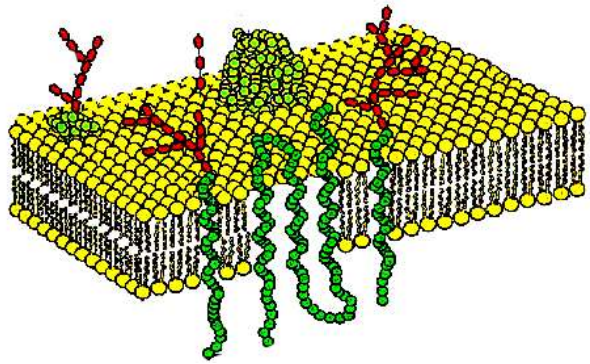
Unlike other drugs interacting with specific membrane receptors with high affinity, general anaesthetics show diverse structures, and their effective concentration at membrane level may be ***mM*** rather than ***nM*.**

It was therefore proposed that general anaesthetic action depends solely on their **physiochemical properties** rather than specific receptor interaction.

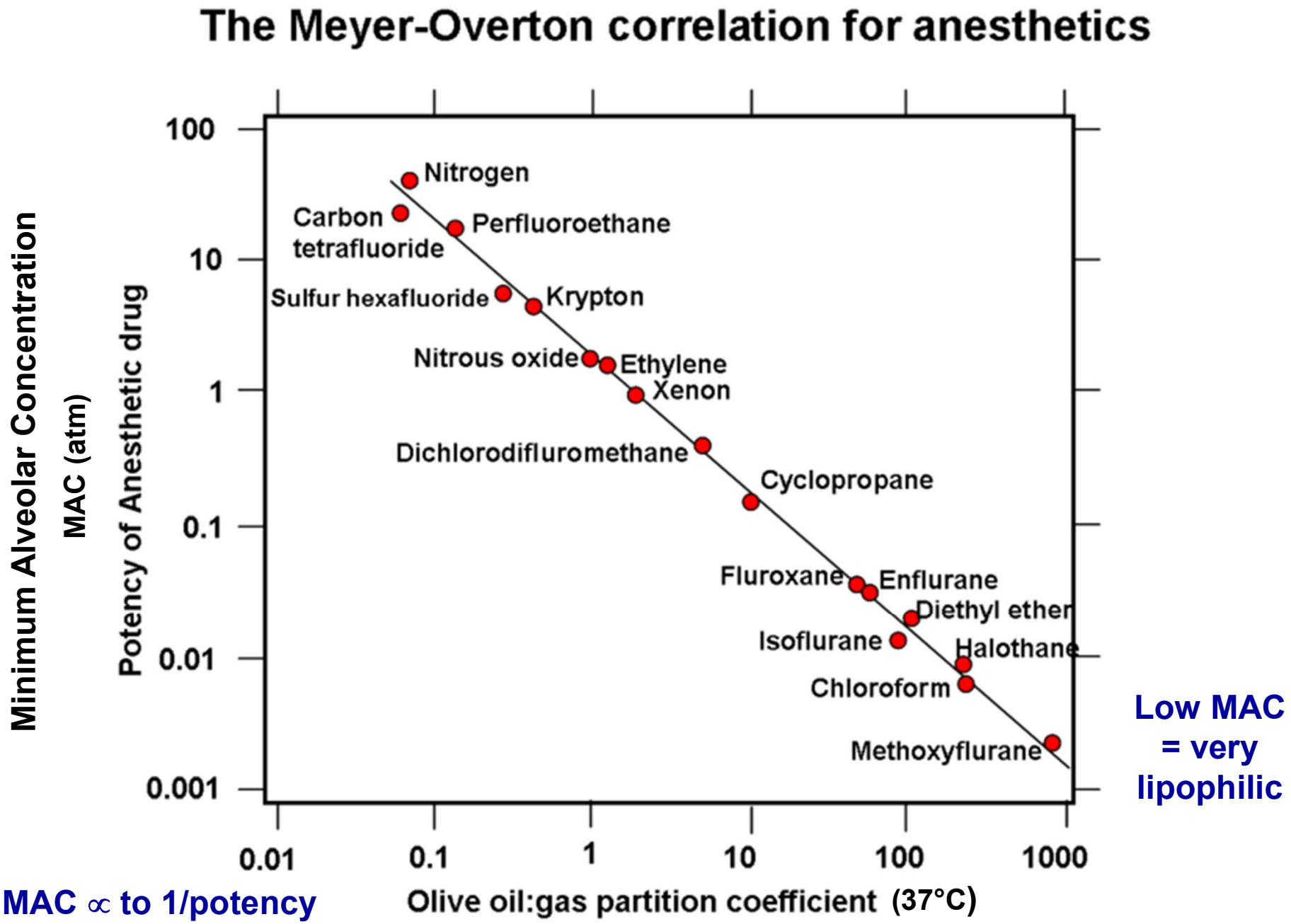
The Meyer–Overton correlation

The Meyer-Overton theory states that the more lipid soluble the drug [olive oil/water partition coefficient], the more potent it is as an anesthetic.

The anaesthetic was believed to simply dissolve and interact with the neuronal lipid membrane, increasing membrane fluidity, and therefore non-specifically altering the function of embedded receptor and ion channel proteins.



The Meyer–Overton correlation



Low MAC = very lipophilic

MAC ∝ to 1/potency

Evidence against lipid solubility theory

1. Not all halogenated ‘membrane–disruptors’ that dissolve in lipid membranes act as anaesthetics, even though the Meyer-Overton hypothesis predicts that they should be.

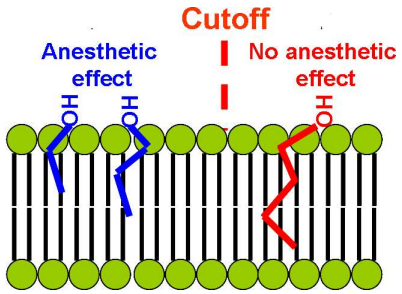
2. Stereoisomers of certain anaesthetics have identical partition coefficients but different anaesthetic potencies *e.g.* **R-(+) etomidate is more potent than the S-(-) isomer.**

3. Some highly lipid soluble agents **(flurothyl)** behave as **convulsants** and not anaesthetics.

Evidence against lipid solubility theory

4. **Altering chain length** of a series of alcohols or hydrocarbons increases their lipid solubility, but at a certain chain length, anaesthetic effectiveness drops **(cut-off effect),** indicating a critical molecular size to still remain effective.

5. **Lipid fluidity effects** produced by general anaesthetics in artificial membranes are very small and mimicked by small changes in temperature (~1°C); such small changes in body temperature do not induce anaesthesia in humans!



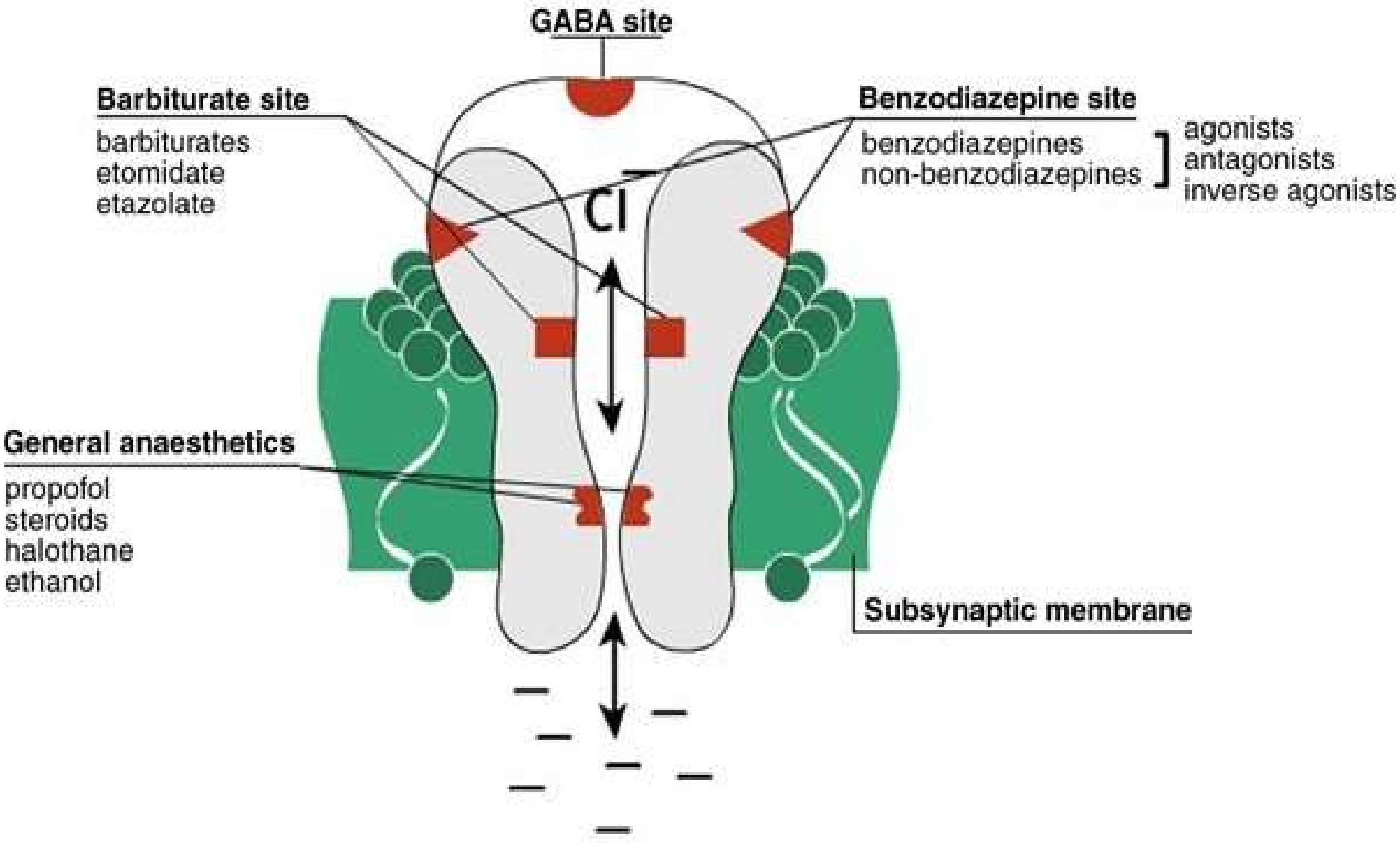
Mechanism of action

Volatile general anesthetics are now thought to interact with specific target neurotransmitter receptors and ion channels.

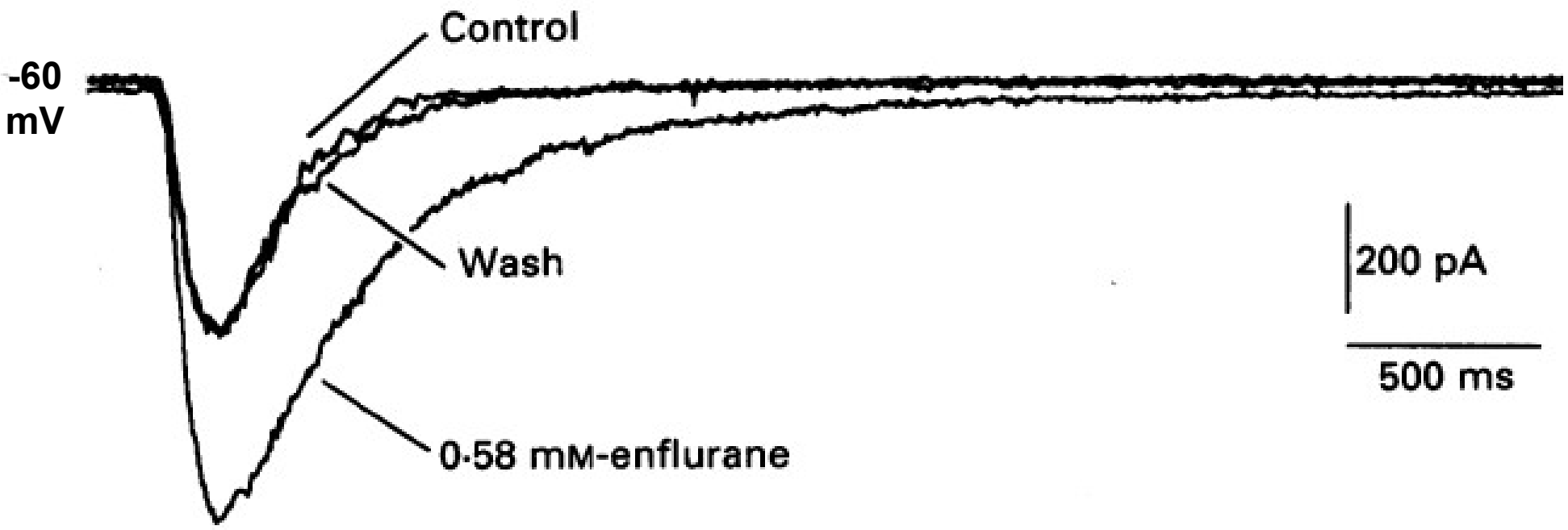
- **$GABA_A$ and glycine receptors** - *enhancing* neuronal Cl^- conductance increase; compounds that are non-anaesthetics do not affect GABA or glycine currents.

- **TASK/TREK-1 (two pore domain) K^+ channels** - *increasing* K^+ conductance →hyperpolarization - ↓in neuronal excitability (halothane/isoflurane).

Interaction of anaesthetics with $GABA_AR$



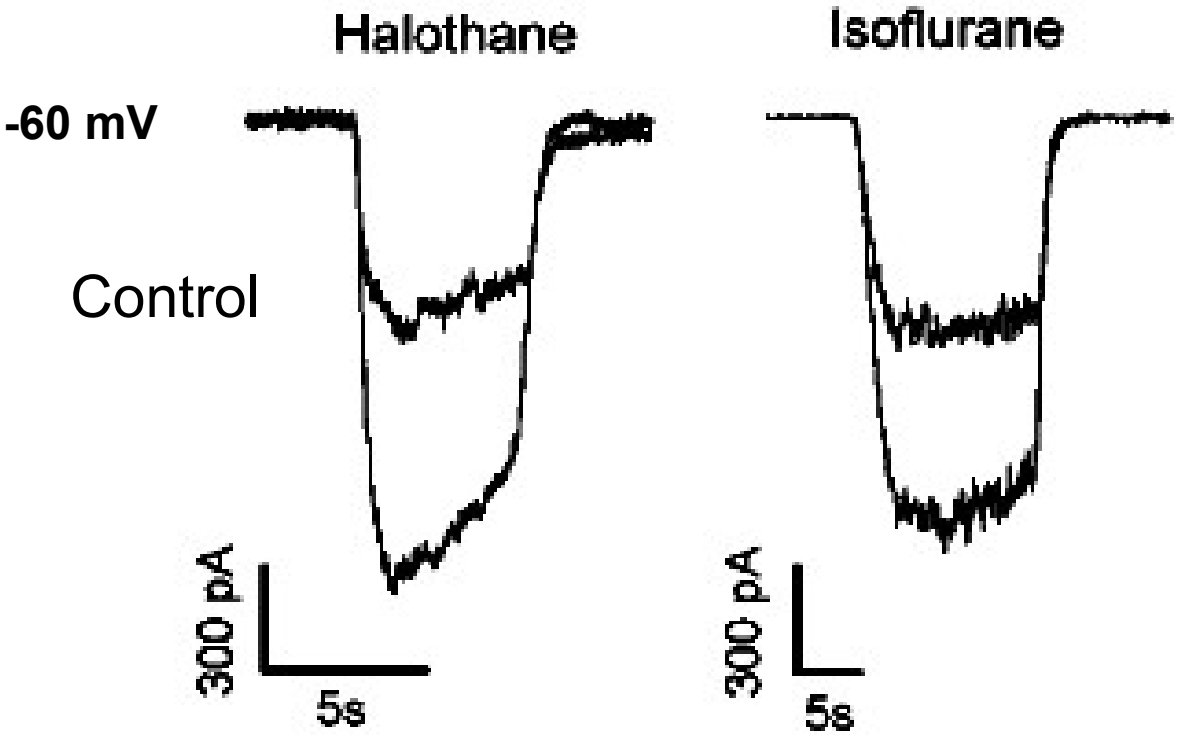
Mechanism of action



Jones et al (1992) J. Physiol 449, 279-293

Reversible enhancement of GABA-evoked inward currents by enflurane recorded under whole-cell patch clamp from a **cultured hippocampal neurone** under voltage clamp at -60 mV holding potential. GABA was applied to the cell body by pressure ejection.

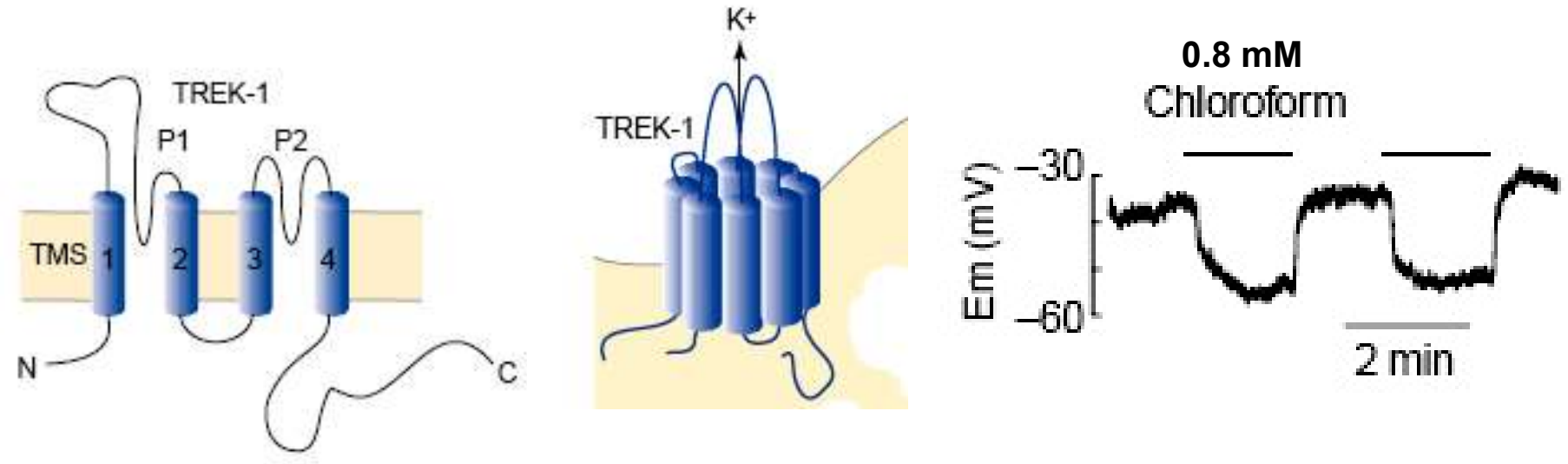
Mechanism of action



Downie et al (1996) Br. J. Pharmacol., 118, 493-502

Potentiation of 10 µM glycine-evoked inward currents by halothane (0.18 mM) and isoflurane (0.31 mM) recorded under whole-cell patch clamp from **rat dissociated medullary neurones** under voltage clamp.

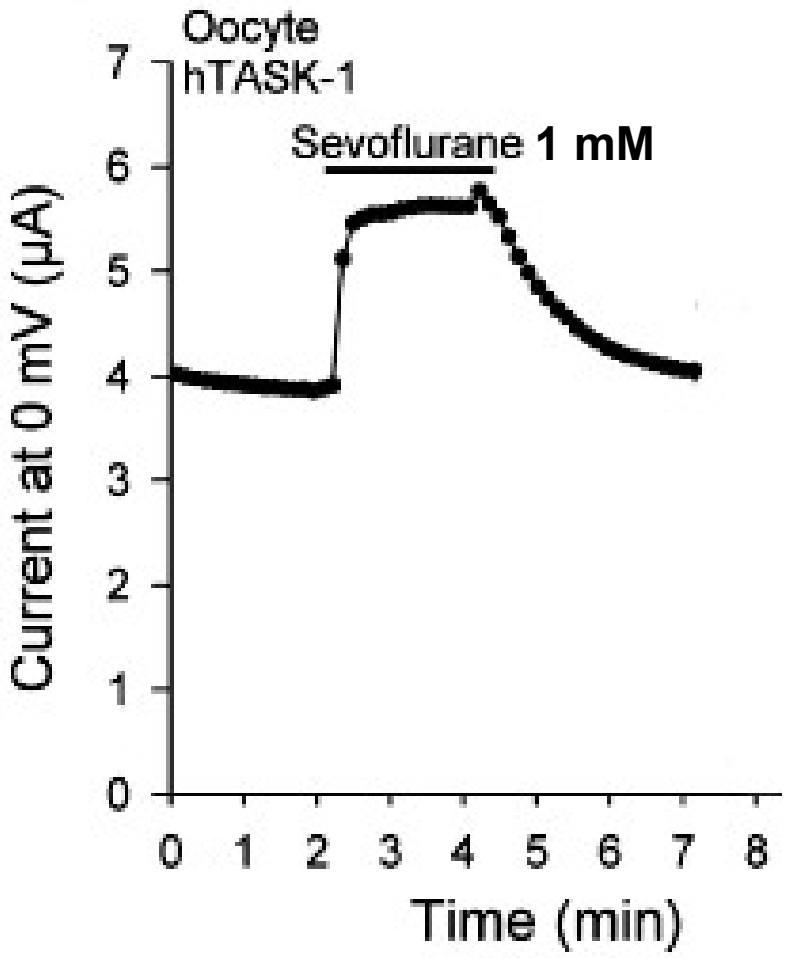
Mechanism of action



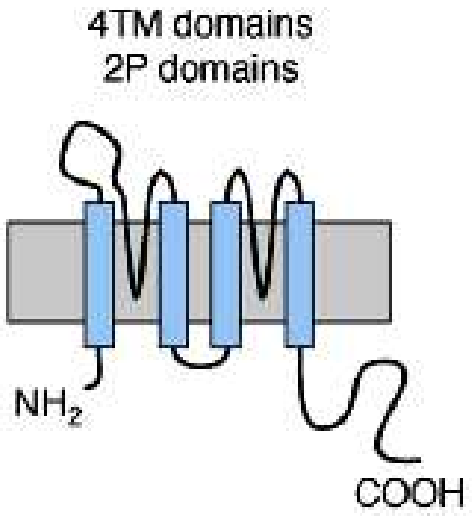
Franks, P & Honore, E. (2004). TIPS: 25, 601-608.

TREK-1 is a K^+ channel formed by a dimer of 4 transmembrane subunits (TMS) that is opened by volatile and gaseous anaesthetics. Trace shows membrane hyperpolarizations produced by chloroform, recorded under whole-cell patch clamp in **transfected COS kidney cells**.

Mechanism of action



TASK-1



Putzke et al (2007) Am J Physiol 293: C1319-C1326.

Outward current produced by sevoflurane (1 mM) recorded under voltage clamp at 0 mV holding potential in an **oocyte transfected with hTASK-1 channels**.

Mechanism of action

Other possible receptor/ion channel targets include:

- **Nicotinic acetylcholine receptors** (nAChRs) (-)

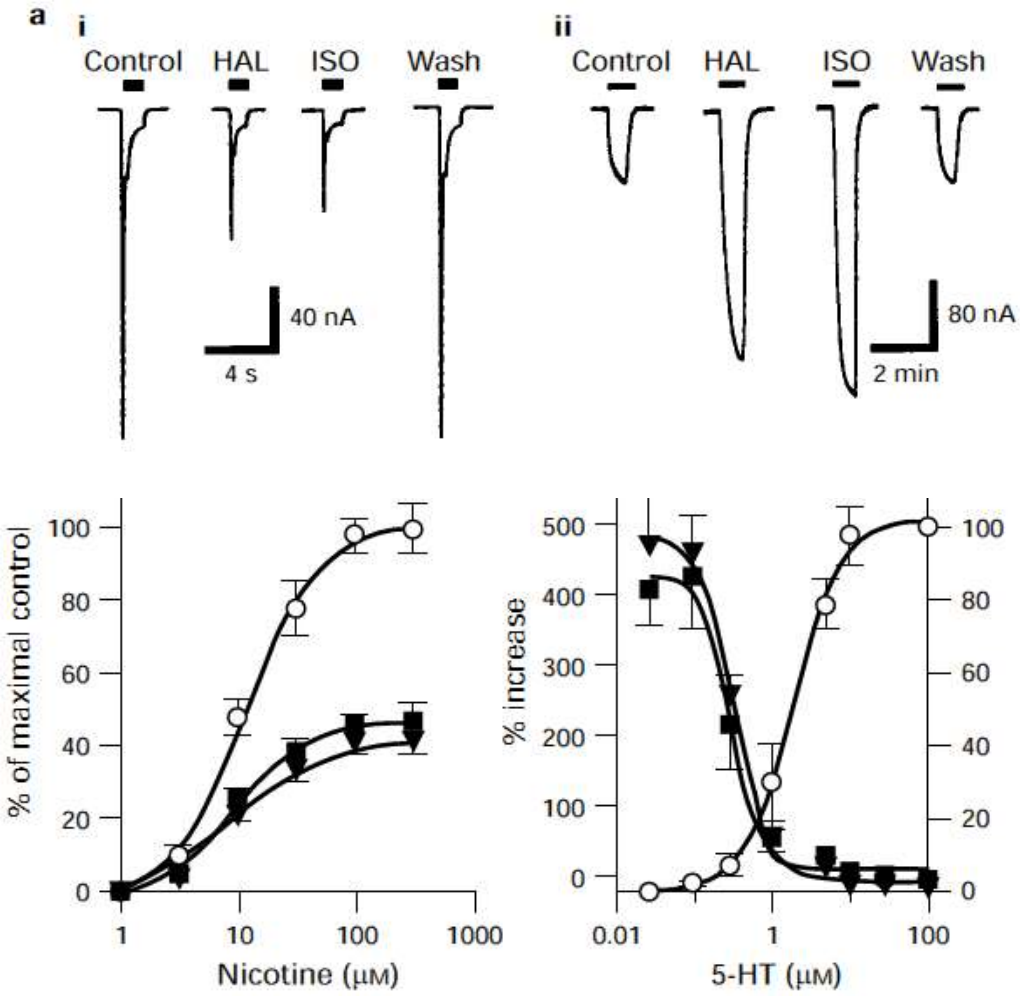
- **Glutamate AMPA or NMDA receptors** (-)

- **$5HT_3$** (ligand-gated)receptors (+) – but there is minimal evidence that $5HT_3$Rs are mediators of anaesthetic action, but they may mediate the nausea/vomiting associated with anaesthetics.

- **Voltage-gated Na^+ ion channels** (weak) - decreasing action potential propagation (-)

- **Voltage-gated Ca^{2+} ion channels** (weak) (-)

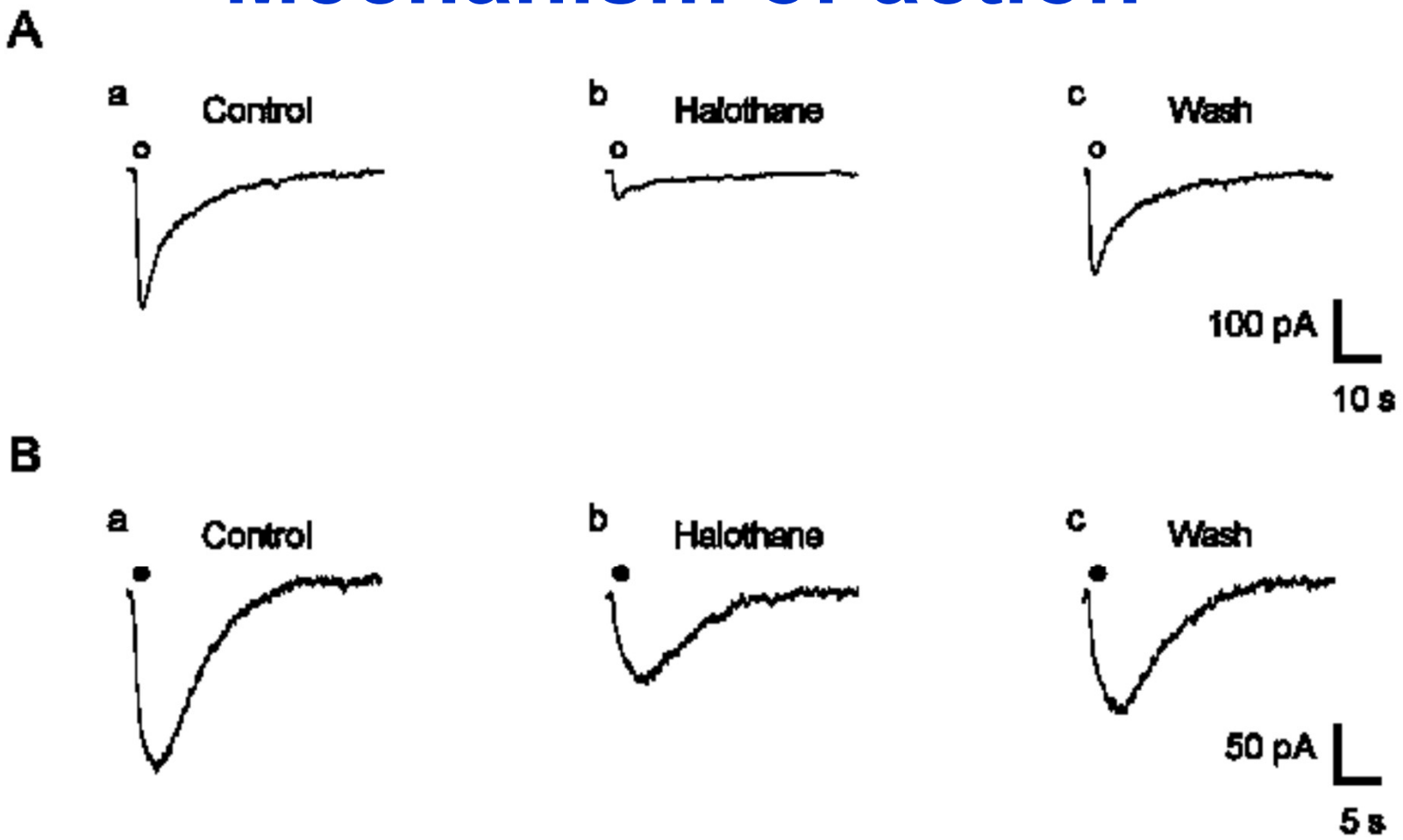
Mechanism of action



Zhang et al (1997) Br. J. Pharmacol.,120, 353 -355

(a) Effects of halothane and isofurane on inward current responses mediated by α7 nAChRs (i) or 5-HT$_3$Rs (ii) expressed **in *Xenopus* oocytes**. Currents were activated by 10 μM nicotine or 0.1 μM 5-HT. (b) Dose-response curves for nACh α7 Rs (i) and 5-HT$_3$Rs (ii) and effects of 5 mM halothane (■) or isoflurane (▼); *n*=5-7 cells.

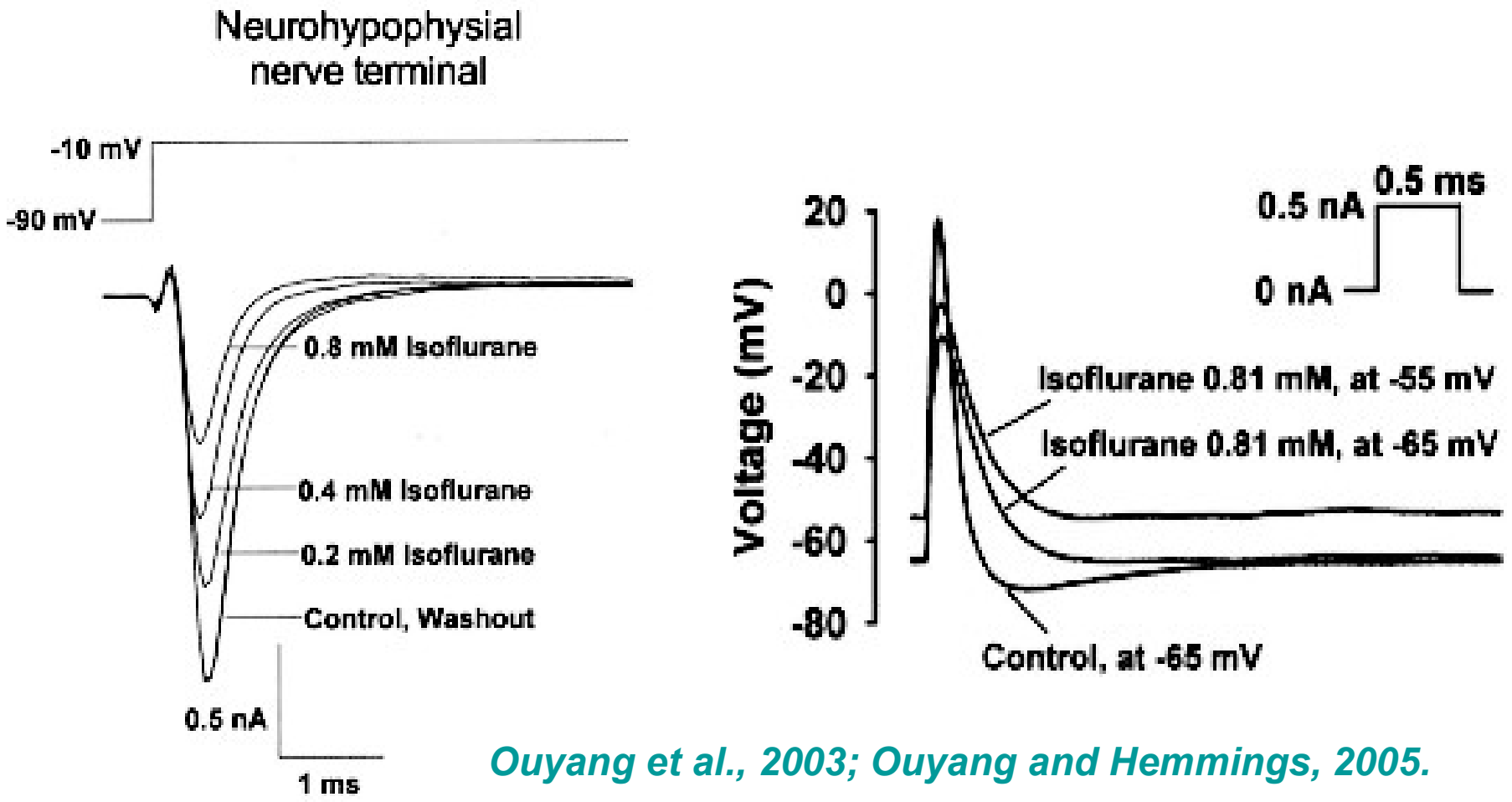
Mechanism of action



Kirson et al (1998) Br. J. Pharmacol 124, 1607-1614

Halothane preferentially blocks currents evoked by AMPA iontophoresis in mouse hippocampal neurones. Whole-cell currents were evoked at -60 mV by iontophoretic application of either AMPA (in 100 µM APV) (A) or NMDA (in Mg^{2+}-free saline + 5 µM CNQX) (B). Traces show control (a), after 15 min in 3.85 mM halothane (b), and after recovery from halothane (c).

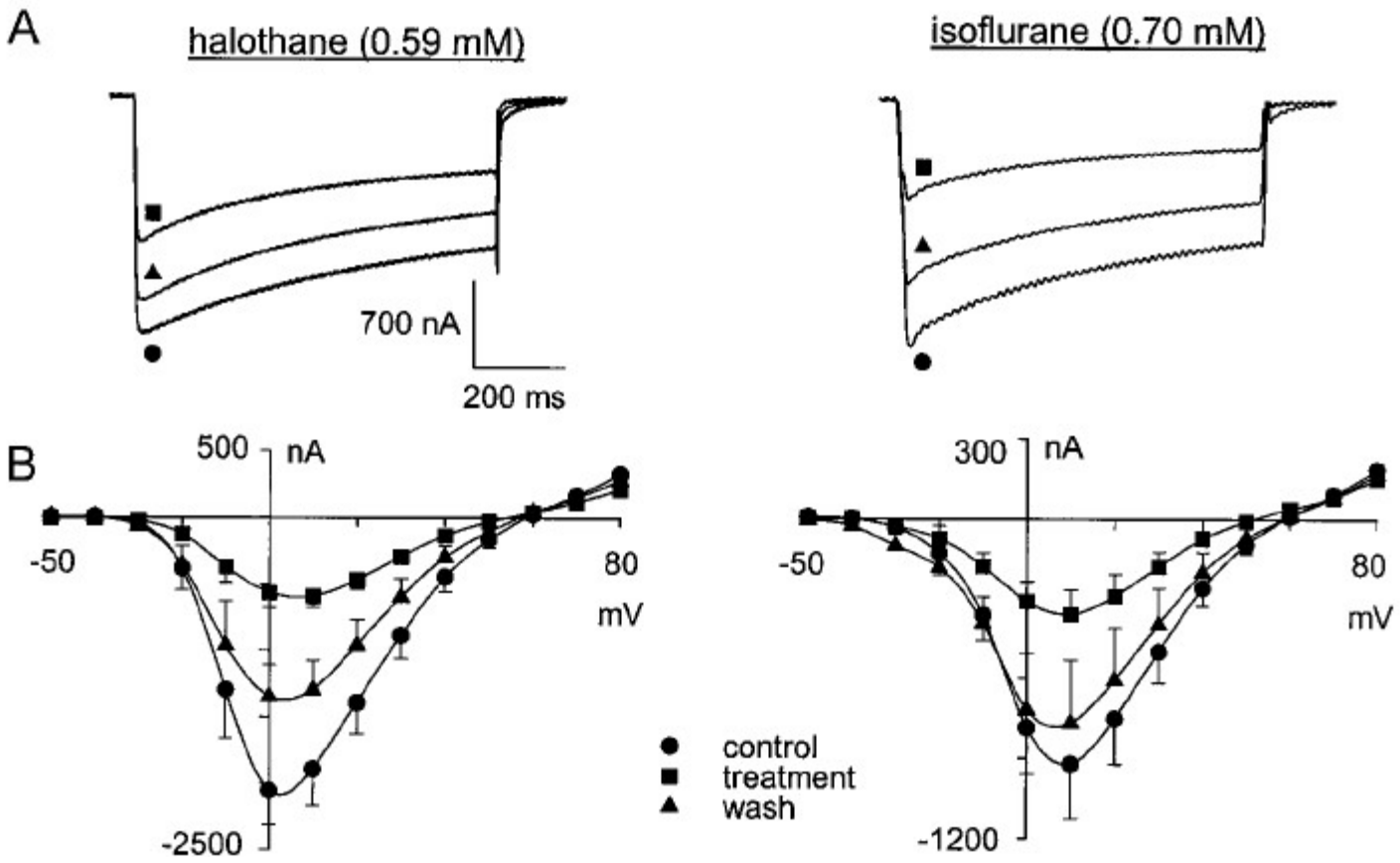
Mechanism of action



Ouyang et al., 2003; Ouyang and Hemmings, 2005.

Volatile anesthetics inhibit Na^+ channels: Electrophysiological recordings of **isolated rat neurohypophysial nerve terminals** show a reversible block of inward Na^+ currents (A) and action potentials evoked by small current injections (B) at clinically relevant concentrations of isoflurane (0.2-0.8 mM). Anaesthetics may therefore inhibit presynaptic neurotransmitter release via this mechanism.

Mechanism of action



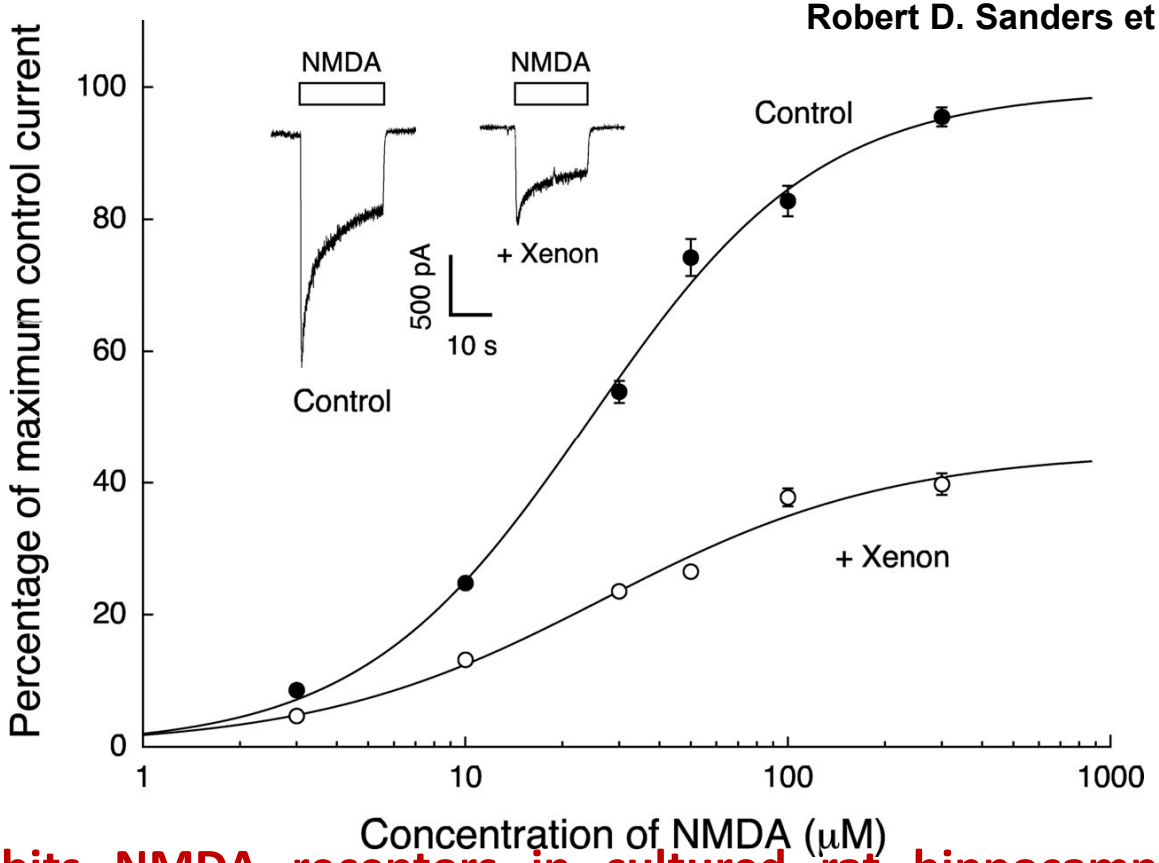
Kamatchi et al., 2001. J Pharmacol Exp Ther. 297(3):981-990.

Effects of halothane or isoflurane on L-type Ca^{2+} channels expressed in *Xenopus* oocytes. (A) Inhibition of barium currents by volatile anaesthetics (superfused for 2 min) recorded under voltage clamp (-80 mV) and washout after 4 min. (B) Peak I-V plots. Oocytes were stepped from -80 to potentials between -50 to 100 mV (450 ms); *n*=7. This mechanism could contribute towards cardiotoxic effects of anaesthetics.

Mechanism of action

Xenon inhibits NMDA receptors in cultured rat hippocampal neurons.

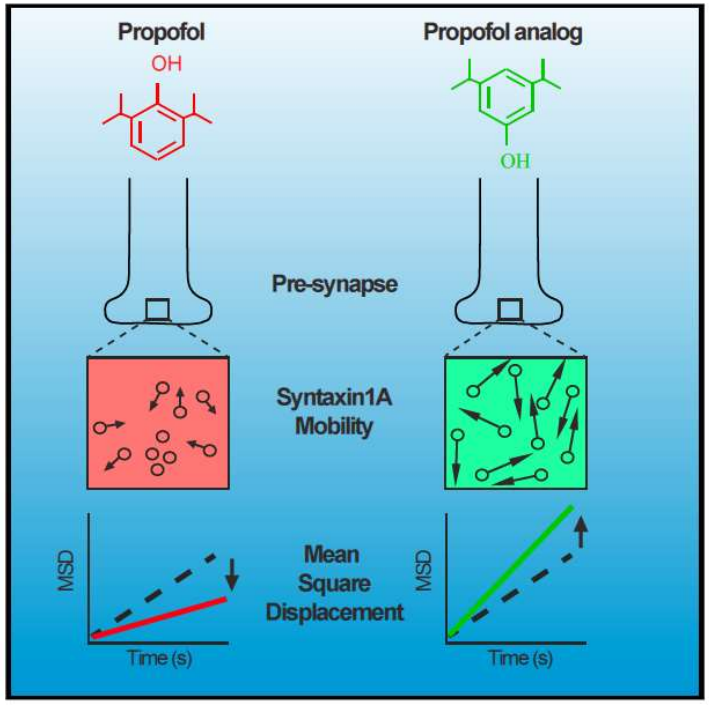
Robert D. Sanders et al. Br Med Bull 2005;71:115-135



Xenon inhibits NMDA receptors in cultured rat hippocampal neurones. NMDA activates an inward current (in neurons clamped at −60 mV) with an EC_{50} of 24 ± 2 μM NMDA. Xenon (80%) inhibited the current by ~60%, but did not significantly change the EC_{50}. Each data point represents mean peak current from at least six cells. Inset shows typical current traces (100 μM NMDA) in the presence and absence of xenon. **Reproduced from Franks et al., Nature, 396, 324, 1998.**

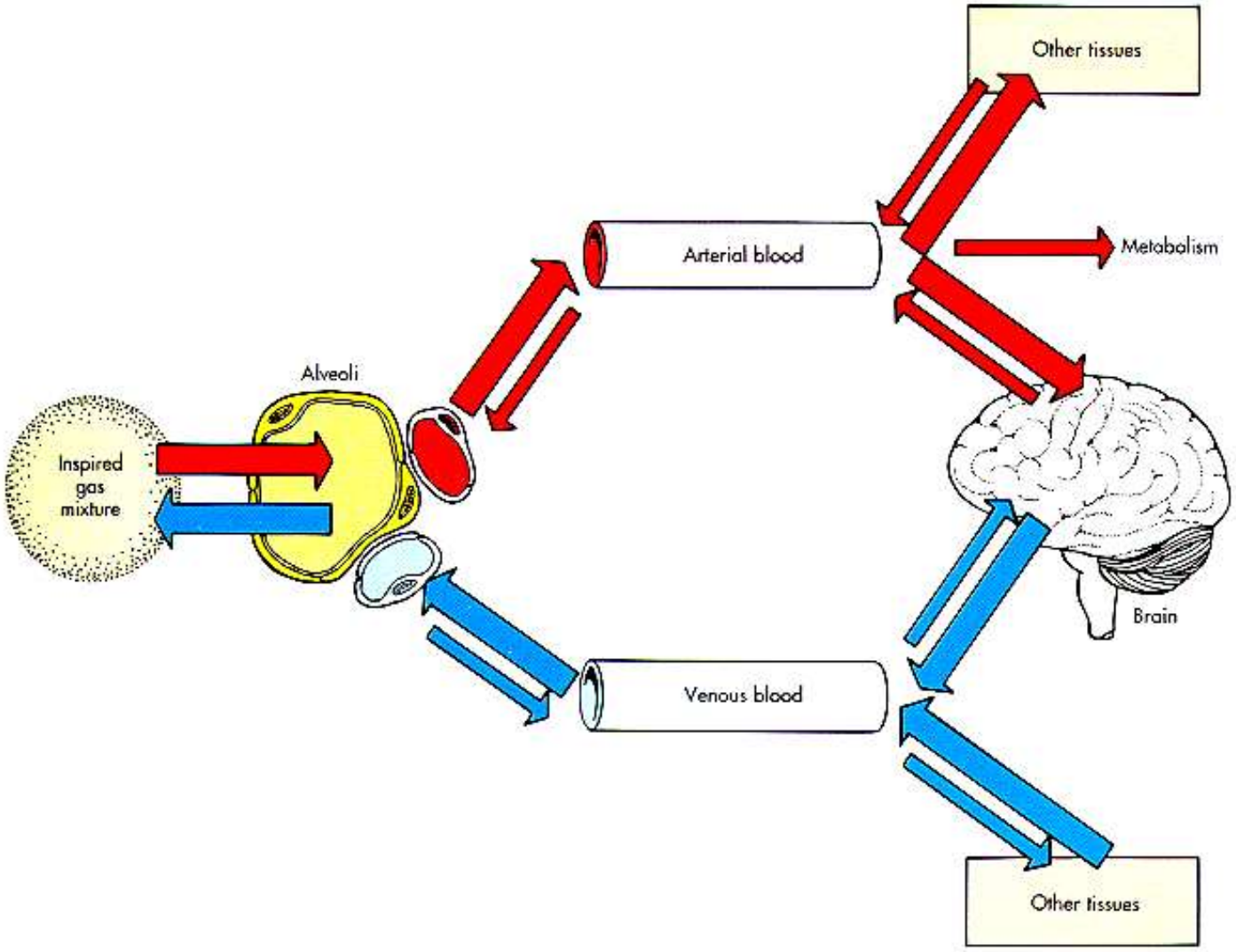
Mechanism of action

Propofol and **etomidate** at clinically-relevant concentrations, have recently been shown to restrict the movement of ***syntaxin 1A*** in neurones, a key membrane-bound SNARE protein required for neural exocytosis – thus, general anaesthetics could also be affecting synaptic transmission and connectivity in the brain as part of their mechanism of action. This could have implications for anaesthesia production in people with disturbed or immature brain connectivity *e.g.* people with Alzheimer's or Parkinson's disease as well as the very young and elderly.



Bademosi et al., 2018. Cell Reports, 22, 247-440.

Bioavailability of inhaled anaesthetics



An inhaled anaesthetic first enters the lungs, then is carried in the blood circulation to all tissues of the body, including the brain; the partial pressure of the anaesthetic in the brain then causes anaesthesia.

Bioavailability of inhaled anaesthetics

The clinical speed of onset and effectiveness of an inhaled anesthetic will therefore be principally governed by its pharmakokinetic properties: -

- The solubility of anaesthetic in the blood **(blood/alveolar gas ratio):** a *low* ratio → less agent buffered in circulation →more available to brain.

- The amount of anaesthetic that reaches the brain **(oil/alveolar gas ratio):** a *high* ratio → more anaesthetic gets to the brain.

Bioavailability of inhaled anaesthetics

Blood/gas ratios (λ): N_2O = 0.47; Halothane = 2.3; Isoflurane = 1.4.

N_2O has low solubility in the blood, thus quickly reaches high concentrations (high arterial tension) and therefore, gets to brain quickly.

Oil/gas ratios: N_2O = 1.4; Halothane = 225; Isoflurane = 98

Halothane and isoflurane are clearly more lipid soluble than N_2O, therefore would partition more readily into the brain.

Anaesthetic potency

The potency of inhaled anaesthetics is usually expressed as **Minimum Alveolar Concentration (MAC)** – defined as *the lung alveolar concentration of anaesthetic vapour (expressed as a percentage volume at 1 atmosphere in O_2, i.e. % partial pressure), needed to prevent a* ***movement*** *response to a standardised painful surgical stimulus [skin incision in forearm] in 50% of patients ≡ ED_{50} of the anaesthetic.*

MAC ∝ 1/potency - *i.e.* *a* <u>low</u> MAC means = *high* anaesthetic potency

e.g. Halothane 0.75%; Isoflurane 1.17%; Sevoflurane 1.6%; Desflurane 6.6%; N_2O 104%

Use of general anaesthetics

Volatile inhalational anaesthetics

Volatile anaesthetics are commonly used for induction and maintenance of anaesthesia and after induction with an i/v anaesthetic - administered through a calibrated vaporizer with air, O_2, or N_2O/O_2.

Induction is rapid, duration short, depending on pharmacokinetic redistribution of the anaesthetic drug from brain to other tissues.

Side effects: **malignant hyperthermia*,** hepato/ nephrotoxicity, cardiorespiratory depression, ↓BP, cardiac arrhythmias - postoperative nausea and vomiting.

*High temperature, tachycardia, hyperventilation, acidosis, muscle rigidity, hyperkalaemia

Use of general anaesthetics

Volatile inhalational anaesthetics -MH

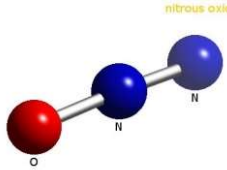
A rare but potentially life-threatening inherited condition called **malignant hyperthermia (MH)** can affect some surgical patients who receive inhalational anaesthetic drugs. ~ 1 in 10,000 persons have a genetic susceptibility to MH; most unaware unless they receive general anaesthesia. A new genetic blood test can detect specific mutations linked to MH. The most commonly affected gene is **RYR1* (ryanodine receptor 1).** If a patient has this genetic susceptibility, they can substitute other anaesthetics for surgery. A range of other genetic conditions are also linked with anaesthesia complications, some relatively common (*e.g.*, Down's syndrome). ***Mutations in RyR1 (a skeletal muscle Ca^{2+} release channel), *hyperactivate* the channel to cause excessive release of i.c. Ca^{2+} and MH following anaesthetic exposure. Dantrolene sodium (muscle relaxant) is the currently approved drug for treating MH.**

Use of general anaesthetics

Volatile inhalational anaesthetics

N_2O - colourless, odourless, tasteless, sweet-smelling inert gas - low blood solubility (rapid induction and recovery) - *weak* anaesthetic potency – but powerful analgesic effects; minimal effects on HR, BP, respiration or liver function - very safe to use for maintenance of anaesthesia. Can be combined (50-66% in O_2) with other inhalational or i/v agents to produce full anaesthesia. Used 50:50% v/v with O_2 for analgesia in obstetrics.

N_2O inhibits NMDARs→produces euphoric/hallucinatory effects. Prolonged exposure can produce **megaloblastic anaemia*.**

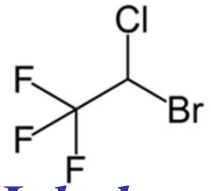


*A condition in which the bone marrow produces unusually large, structurally abnormal, immature red blood cells (megaloblasts).

Use of general anaesthetics

Volatile inhalational anaesthetics

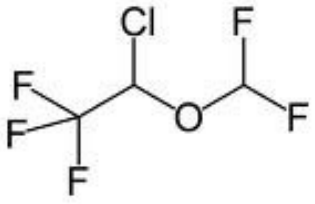
Halothane: potent, non-flammable and non-irritant; rarely used now because or risk of severe hepatotoxicity after repeated exposure.



Halothane

Isoflurane: Most widely used agent with O_2 or N_2O; stable, colourless, non-flammable; minimal cardiac effects; no hepatotoxicity; systemic vasodilation possible; **can be quite irritant**, causing cough and laryngospasm.

Isoflurane

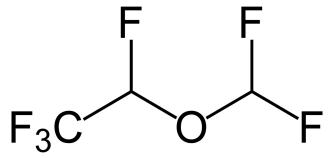


Use of general anaesthetics

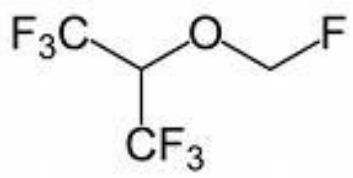
Volatile inhalational anaesthetics

Desflurane: rapidly acting and rapid recovery but less potent than isoflurane; **quite irritant to airways** so less commonly used; no malignant hyperthermia.

Sevoflurane: rapidly acting and more potent than desflurane; quick recovery; **non-irritant**; little effect on heart rhythm; often used for induction.



Desflurane



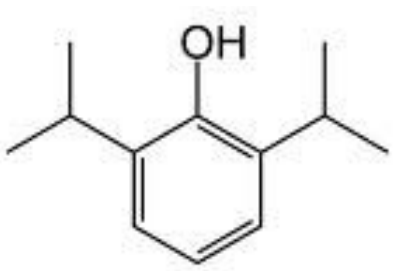
Sevoflurane

Use of general anaesthetics

Intravenous anaesthetics

Propofol: highly lipid-soluble; widely used for maintenance of anaesthesia during surgery, and for pre-sedation; fast acting/short duration; no analgesia; antiemetic. **Acts by potentiating $GABA_A$ and glycine effects in the brain.**

Side effects: respiratory depression, bradycardia, ↑BP, anaphylaxis, convulsions. i/v injections can be painful.



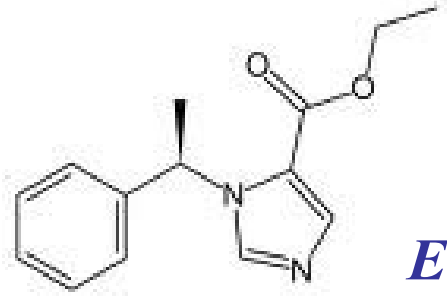
Propofol

Use of general anaesthetics

Intravenous anaesthetics

Etomidate: non-barbiturate – no analgesic properties; minimal cardiovascular or respiratory side effects, but depresses adrenal corticosteroid production, so not used for maintenance of anaesthesia. Can induce amnesia at low doses. **Acts by enhancing $GABA_A$-mediated inhibitory responses.**

Side effects: pain at injection site, temporary muscle movements, fast or slow breathing, hiccups, snoring, ↑ or ↓BP, fast or slow heart rate, arrhythmias, and postoperative nausea or vomiting.



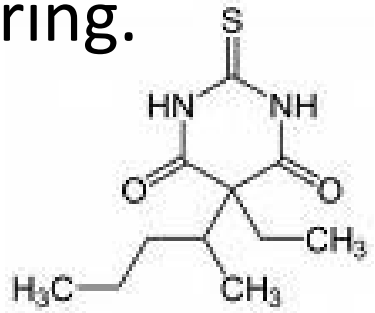
Etomidate

Use of general anaesthetics

Intravenous anaesthetics

Thiopental Na (pentothal): – rapidly acting (lipid soluble) – rapidly crosses BBB – rapid diffusion out of brain - rapid recovery; decreases BP and respiration; no analgesic action. Used in combination with inhaled anaesthetics. **Acts mainly to prolong $GABA_A$-mediated inhibitory responses; also blocks glutamate receptor–mediated effects.**

Side effects: coughing, sneezing, hiccups, slowed breathing, slow heart rate, cardiac arrhythmias, prolonged sleepiness and recovery, and shivering.



Thiopental

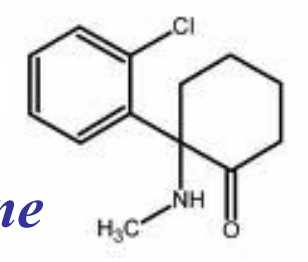
Use of general anaesthetics

Intravenous anaesthetics

Ketamine: - similar to PCP (phenylcyclidine)- produces 'dissociative' anaesthesia - catatonia (no talking or reacting), amnesia, analgesia; hallucinations and vivid dreams; emergence delirium. Can be used for short ops (mainly for paediatric anaesthesia), - has serious abuse potential. **It stimulates the cardiovascular system, therefore good for emergency patients in shock.**

Chronic abuse can cause *irreversible bladder damage*

Acts by blocking NMDAR channels at the 'PCP site' in use-dependent manner; also inhibits nAChRs (β4) and Na^+ channels.



Ketamine

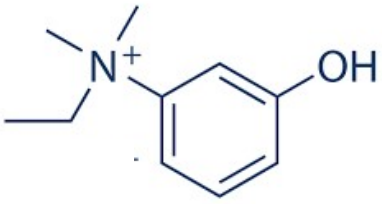
Supplementary (adjunct) drugs used in general anaesthesia

Anaesthesia adjunct medications - are additional drug treatments used to increase the efficacy or safety of a primary general anaesthetic.

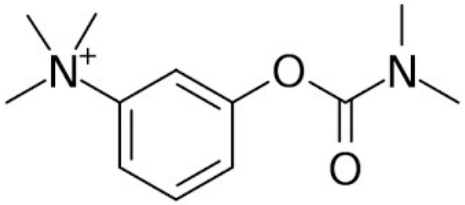
- **Opioid analgesics: *e.g*. fentanyl, alfentanil, remfentanil**; (given as i/v premedications + intermittent boluses)- used to lower the amount of inhalant anaesthetics required to achieve effective analgesia during induction/maintenance of general anaesthesia - also for post-op analgesia: rapid onset and short duration of action; potent analgesia, loss of interest in environment, with no loss of consciousness, but can produce nausea/vomiting, respiratory and cardiovascular depression and muscle rigidity (chest/jaw).

Supplementary (adjunct) drugs used in general anaesthesia

- **Competitive (aminosteroid) neuromuscular blocking agents *e.g.*** **atracurium, rocuronium, pancuronium, vecuronium**: given i/v as supplementary agents administered with general anaesthetics (together with artificial respiration) in order to produce skeletal muscle relaxation of controlled duration to facilitate abdominal surgery (minimize dose of general anaesthetic required) and also for easier insertion of endotracheal tubes. Reversal of competitive neuromuscular blockers after surgery, can be made by administering **anticholinesterases i/v *e.g.*** **edrophonium, neostigmine** (together with Atropine to prevent muscarinic side-effects- see below).

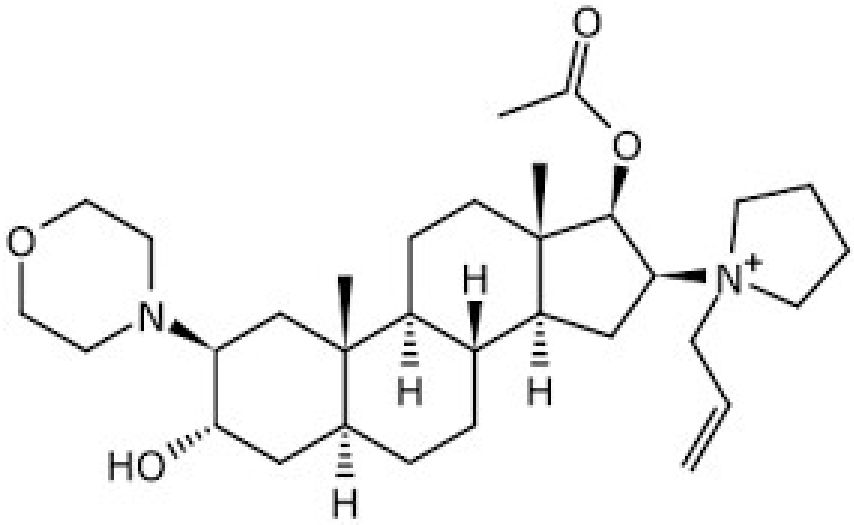


Edrophonium

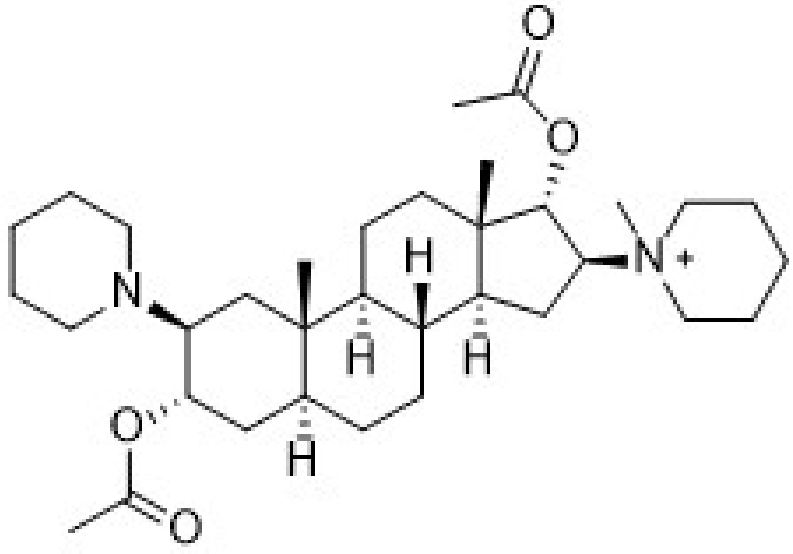


Neostigmine

Supplementary (adjunct) drugs used in general anaesthesia



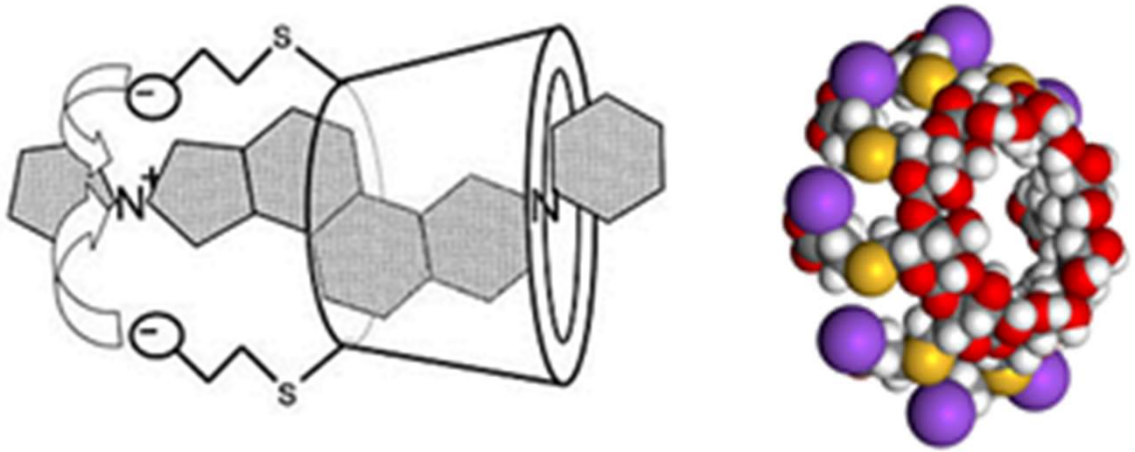
Rocuronium



Vecuronium

Supplementary (adjunct) drugs used in general anaesthesia

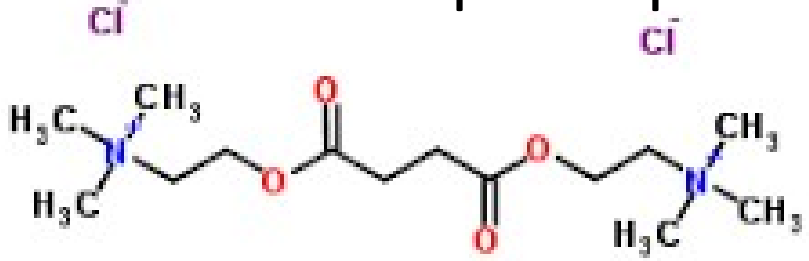
- In 2008, **Sugammadex** was introduced (see: Welliver et al., (2008). Drug Des Devel Ther. 2: 49–59). It is a modified γ-cyclodextrin, with a lipophilic core and a hydrophilic periphery, which is used to rapidly reverse neuromuscular blockade after administration of rocuronium or vecuronium. Since it is not an AChE, muscarinic cholinergic side effects are not produced on reversal, so co-administration of an antimuscarinic agent is not required.



A sugammadex molecule encapsulating a rocuronium molecule.

Supplementary (adjunct) drugs used in general anaesthesia

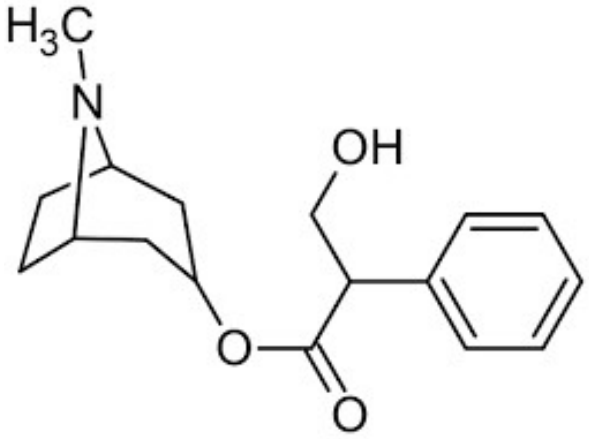
- **Non-competitive (depolarizing) neuromuscular blockers:** ***e.g.*** **Suxamethonium:** (ultra-short acting), given i/v, is used in conjunction with general anaesthesia as a skeletal muscle relaxant to facilitate rapid tracheal intubation and mechanical ventilation in short surgical procedures. Since suxamethonium is normally metabolised by plasma pseudo cholinesterase, prolonged paralysis can occur in patients with abnormal plasma cholinesterases. It can also trigger malignant hyperthermia in some susceptible patients.



Suxamethonium

Supplementary (adjunct) drugs used in general anaesthesia

- **Antimuscarinic drugs: *e.g.* atropine, glycopyrronium or hysoscine** can be given as premedications (i/m) to dry up bronchial and salivary secretions to facilitate intubation and inhalational anaesthesia - also used to prevent excessive muscarinic effects: (bradycardia, salivation) following administration of AChEs in neuromuscular block reversal. Hyoscine can also have useful sedative, amnesic and anti-emetic effects.



Atropine

Supplementary (adjunct) drugs used in general anaesthesia

- **Benzodiazepines: ($GABA_A$ receptor modulators): *e.g.* diazepam, lorazepam, midazolam, temazepam:** are used i/v or i/m: as premedications to produce relief of anxiety, sedation and amnesia before major surgery; also for induction; no analgesia; can produce respiratory depression.
- **$5HT_3R$ antagonists; *e.g.* odansetron, granisetron:** commonly given pre-op to prevent post-op nausea and vomiting following inhalational general anaesthesia.
- **Hypnotics ($GABA_A$ receptor modulators) *e.g.* propofol, etomidate *i/v* (see above):** can be given for induction of anaesthesia, supplementary to N_20 for short surgical procedures.

Supplementary (adjunct) drugs used in general anaesthesia

- **Opioid analgesic: *e.g.* remifentanil:** Remifentanil, is a potent, ultra short-acting synthetic opioid analgesic drug. It is given to patients during surgery as an adjunct to an anaesthetic to relieve pain. Remifentanil induces a deeper analgesia and anaesthesia. Patients given remifentanil show faster recovery times but may need post-operative analgesia more frequently because of the rapid offset of action.
- **Remifentanil** is different from all other opioids in that it possesses an ester linkage that allows it to be hydrolysed relatively quickly *in vivo* by non-specific blood and tissue esterases thus, it may be particularly useful where rapid onset and offset of opioid effects are desirable.