volatile general anaesthetics which lead to neuroprotective effect. According to a recent study with knockout animals, TREK-1 channels might play an important role in the general anaesthetic effect of volatile anaesthetics, such as halothane, providing an explanation for the neuroprotective effect of general anaesthetics.

Potassium channels have been thought to regulate potential in the mitochondrial membrane, respiration rhythmic generation and ion homeostasis. For neuroprotective effects, some potassium channels have been identified in the inner mitochondrial membrane: the KATP channel, the BK (Ca^{2+}) channel (large conductance Ca^{2+} regulated K^+ channels), the voltage-gated K^+ channel 1.3 (Kv1.3) channel, as well as the TASK-3 channel. It has been demonstrated that potassium influx to the brain mitochondria by the KATP channel or the BK channel could produce neuroprotective effects on neuron survival under ischaemia.

Hyperpolarisation-Activated Cyclic Nucleotide (HCN) CHANNELS

Structure and function of HCN channels

Hyperpolarization-activated cyclic nucleotide (HCN) gated channels conduct HCN current, that contributes to multiple membrane properties governing cellular excitability'.[23–25] Conventional HCN1 knockout mice were used to test directly the contributions of specific HCN subunits to the effects of isoflurane, an inhalational anaesthetic, on membrane and integrative properties of motor and cortical pyramidal neurons *in vitro*. Compared with wild-type mice, residual. If from knockout animals was smaller in amplitude and presented with HCN2-like properties. Isoflurane increased temporal summation of excitatory postsynaptic potentials (EPSPs) in cortical neurons from wild-type mice, an effect predicted by simulation of anaesthetic-induced dendritic inhibition. Accordingly, anaesthetic-induced EPSP summation was not observed in cortical cells from HCN1 knockout mice. In wild-type mice, the enhanced synaptic summation observed with low concentrations of isoflurane contributed to a net increase in cortical neuron excitability. Inhibition of HCN1 by anaesthetics in cortical neurons has been shown to contribute to the synaptically-mediated slow-wave cortical synchronization that accompanies anaesthetic-induced hypnosis.[26]

Na^+ CHANNELS AND GENERAL ANAESTHESIA

Structure and function of Na^+ channels

The sodium channel family has nine homologous pore-forming α-subunits and these subunits show distinct cellular and subcellular distribution, depending on different species and tissues.[27] The pore forming component of sodium channels is a 260 kDa glycoprotein α-subunit, with large intracellular N- and C-terminal. Four internally homologous repeated domains are contained in this subunit (I–IV) and over 50% of the sequence of these domains has been identified. It has been demonstrated that six segments (S1-S6) are contained in each domain and that they form transmembrane α-helices. In addition, four integral membrane glycoprotein subunits have been identified. Generally, the α-subunit is sufficient for the basic functions of sodium channels while expression of β-subunits regulates inactivation.

Generally, two principal mechanisms contribute to the inhibition of Na^+ channel by volatile anaesthetics. These are voltage-independent block of peak currents and enhanced inactivation due to a hyperpolarizing shift in the voltage dependence of steady-state fast inactivation. There are significant differences between isoforms in the contributions of each mechanism to overall inhibition. Volatile anaesthetics, also inhibit native neuronal and nerve terminal Na^+ channels, supporting the notion that depression of synaptic neurotransmitter release occurs by Na^+ channel blocking.[28, 29]

VESICULAR TRANSPORT

A portion of the plasma membrane is invaginated, coated with molecules of the protein clathrin, and pinched off forming a membrane-bounded **vesicle** called an endosome. A **vesicle** is a small, spherical compartment that is separated from the cytosol by at least one lipid bilayer. Many **vesicles** are **made** in the Golgi apparatus and the endoplasmic reticulum, or are **made** from parts of the cell membrane by endocytosis. There are **three types** of endocytosis or vesicular transport mechanisms and they are:

a. Pinocytosis
b. Phagocytosis vesicular transport is the proposed process for the absorption of orally administered Sabin polio vaccine and large proteins. Transport of proteins, polypeptides like insulin from insulin producing cells of the pancreas into the extracellular space.
c. Receptor-mediated endocytosis—Neuronal intracellular transport is performed by motor proteins, which deliver vesicles, organelles and proteins along cytoskeletal tracks inside the neuron. The propofol-induced effect on vesicle transport was reversible and blocked by the $GABA_AR$ antagonist gabazine in low concentration. Propofol causes vesicle

anaesthetic blockade than large, myelinated (A) fibers conducting touch. However, experimental studies reveal a more complex picture. *In vivo* studies of sciatic nerve block in rats with lidocaine indicate that larger A fibers are more susceptible to tonic and phasic block than smaller C fibers. Differential block of large and small nerve fibers is also affected by choice of local anaesthetic. Those with an amide group, high pK a , and lower lipid solubility are more potent blockers of C fibers. Thus, experimental studies indicate that local anaesthetic block of nerve fibers will intrinsically depend on type (size) of fiber, frequency of membrane stimulation, and choice of local anaesthetic. During clinical applications, the exposure length of the nerve fiber may explain differential block, as small nerve fibers require a shorter length of fiber exposed to local anaesthetic for block to occur than do large fibers. It is theorised that this observation is because of decremental conduction block of a "critical length" of nerve. Decremental conduction describes the decreasedability of successive nodes of Ranvier to propagate an impulse in the presence of local anaesthetic. As internodal distances become greater with increasing nerve fiber size, larger nerve fibers will demonstrate increasing resistance to local anaesthetic block. Evidence for this mechanism is conflicting. Sciatic nerve blocks in rats demonstrate greater length of spread along the nerve and greater intraneural content of radio labelled lidocaine with injections of high volume and low concentrations of lidocaine.

Efferent Electrical Activity of Local Anaesthetics

Administration of calcium channel blockers to spinal cord N (neuronal) calcium channels results in hyperpolarisation of cell membranes, resistance to electrical stimulation from nociceptive afferents, and intense analgesia. Local anaesthetics appear to have similar actions on calcium channels, which may contribute to analgesic actions of central neuraxially administered local anaesthetics. In addition to ion channels, multiple neurotransmitters are involved in nociceptive transmission in the dorsal horn of the spinal cord. For example, tachykinins (substance P) are important neurotransmitters modulating nociception from C fibers. Administration of local anaesthetics in concentrations that occur after spinal and epidural anaesthesia inhibits postsynaptic depolarisations driven by substance P and may decrease nociception via this inhibitory mechanism. Other neurotransmitters that are important for nociceptive processing in the spinal cord, such as acetylcholine, γ-aminobutyric acid (GABA), and N-methyl-D-aspartate (NMDA), can all be affected by local anaesthetics either pre- or post-synaptically. These studies suggest that anti-nociceptive effects of central neuraxial local anaesthetic block may be mediated via complex interactions at neural synapses in addition to ion channel blockade.

Summary

Most general anaesthetics have remarkably weak affinity for their targets acting at much higher concentrations than most other drugs so that diverse side effects are inevitable. The main handicap to understanding the mechanisms of general anaesthesia is the diversity of chemically unrelated compounds including diethyl ether and halogenated hydrocarbons, gases nitrous oxide, ketamine, propofol, benzodiazepines and etomidate, as well as alcohols and barbiturates. Does this imply that general anaesthesia is caused by many different mechanisms? Until now, many receptors, molecular targets and neuronal transmission pathways have been shown to contribute to mechanisms of general anaesthesia.

Mechanism of action of local anaesthetics and neuraxial anaesthetics produce anaesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves. Sodium influx through these channels is necessary for the depolarisation of nerve cell membranes and subsequent propagation of impulses along the course of the nerve, which are blocked.

References

1. Meyer KH (1937). "Contributions to the theory of narcosis". Trans Faraday Soc. 33:1062–8. doi:10.1039/tf9373301062]
2. Eckenhoff RG, Tanner JW, Johansson JS (1 August 1999). "Steric hindrance is not required for n-alkanol cutoff in soluble proteins". Mol. Pharmacol. 56(2):414–8. PMID 10419562.
3. Cantor RS (December 1997). "The Lateral Pressure Profile in Membranes: A Physical Mechanism of General Anaesthesia". Biochemistry. 36 (9): 2339–44. PMID 9054538. doi:10.1021/bi9627323.
4. McFarlane C, Warner DS, Todd MM, Nordholm L. AMPA receptor competitive antagonism reduces halothane MAC in rats. Anesthesiology. 1992;77:1165–70. [PubMed].
5. Minami K, Wick MJ, Stern-Bach Y, Dildy-Mayfield JE, Brozowski SJ, Gonzales EL, Trudell JR, Harris RA. Sites of volatile anaesthetic action on kainate (Glutamate receptor 6) receptors. J Biol Chem. 1998;273:8248–55. [PubMed].
6. Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia. Nature. 1998; 396:324. [PubMed].
7. Jevtović-Todorović V, Todorović SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4:460–3. [PubMed].

circumvented by administration at a site that avoids the portal circulation such as sublingual or, to some extent, rectal. The degree to which an administered drug reaches the systemic bloodstream is termed its bioavailability (Fig. 2.4).

Uptake after intramuscular or subcutaneous administration is largely dependent on local blood flow rather than ionisation or lipid solubility. The transdermal route can be used for highly lipid-soluble drugs (e.g. GTN, fentanyl), where slow absorption eventually produces sustained blood concentrations.

A fundamentally different pattern of uptake is seen for an inhaled drug in that it crosses the alveolar membrane into the blood along its partial pressure gradient. This produces an exponential wash-in, until at equilibrium (i.e. the partial pressure in blood equals that in the inspired and expired gas) no further net uptake occurs.

A clinical effect requires sufficient uptake to exert an adequate partial pressure in the body tissues; it is achieved most rapidly by and faster speed of onset produced by a low BGPC reflects the smaller number of molecules needed in solution to exert a partial pressure.

Alveolar partial pressure, measurable from end-tidal exhaled gas, closely reflects that of arterial blood and, in turn, that of the brain, enabling continuous monitoring of an indirect measure of drug delivery to the target site.

Distribution

After IV administration of a drug, the peak blood concentration is determined by the dose, the rate of administration, and the cardiac output. With a high cardiac output, the effective volume of blood in which the drug is initially diluted is larger, leading to a lower peak concentration. However, the high cardiac output transports the drug quickly to the vessel-rich tissues (including brain), and for highly lipid-soluble drugs, rapid equilibration occurs, leading to a fast onset of action. It is the high blood supply more than the lipid solubility that explains this.

Conversely, a low cardiac output leads to a higher initial peak concentration, because the drug is mixed with a smaller volume of blood during injection, though it will take longer to reach its target site. This explains why a smaller dose of induction agent is required in an elderly or shocked patient but may have a slower onset of action, while a young patient may require a much larger dose, yet will start to feel the effects more quickly.

Other tissues may also have a high affinity for the drug, but can only take up the drug slowly as they receive a lower proportion of the cardiac output. As they do so, however, the blood concentration decreases, soon falling below the brain concentration, whereupon the drug leaves the brain to be redistributed to other tissues. This redistribution is referred to as the α phase and explains the rapid termination of effect of lipid-soluble drugs such as propofol or thiopental following a bolus dose. As the less well-perfused tissues accumulate more drug, the concentration difference between compartments falls and the rate of redistribution slows in a declining exponential fashion. This also acts to slow down the redistribution if further drug is given, and subsequent doses should therefore be amended accordingly.

For inhalational agents, the pharmacokinetic model for distribution is similar; however, because the rate of administration is slower, the various compartments fill simultaneously, although at different rates depending on their blood supplies. Because there is never a rapid loading dose to anyone compartment, redistribution between compartments is minimal. As administration continues, the vessel-poor and intermediate compartments become progressively saturated, delaying subsequent recovery, particularly for agents with a high lipid solubility.[1]

Elimination

Although the initial effects of a drug may wear off because of redistribution, full recovery depends upon the removal of the drug from the body. Such elimination may result from excretion, metabolism, or a combination of both. Large molecular weight drugs are often excreted in the bile, but most drugs are renally excreted. In order for the kidneys to handle lipid-soluble drugs, they need to be metabolized into a polar, water-soluble form. Most of this metabolism occurs in the liver and can be divided into Phase 1 and Phase 2 reactions. Phase 1 reactions include oxidation, reduction, and hydrolysis; in Phase 2 reactions, the resulting metabolites are conjugated with sulphate, glucuronide, or other groups.

For most drugs, elimination occurs in an exponentially declining manner, the rate of elimination being proportional to the plasma concentration, as the downstream end of the gradient remains at zero. This system (i.e. the amount of drug being removed is a constant fraction in unit time rather than a constant amount) is known as first-order kinetics.

For some drugs, elimination may depend on the action of an enzyme or transporters which can become saturated. Once the relevant blood concentration is reached, elimination becomes constant, limited to a maximum amount in unit time. This is referred to as zero-order kinetics and can result in dangerously high concentrations with continued, unmonitored drug administration. It may be encountered at high concentrations with aspirin, ethanol, phenytoin, or thiopental.

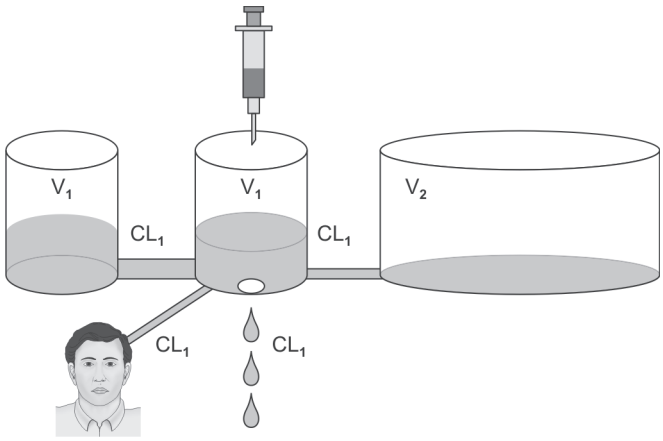

Fig. 2.2: Concept of target-controlled infusion

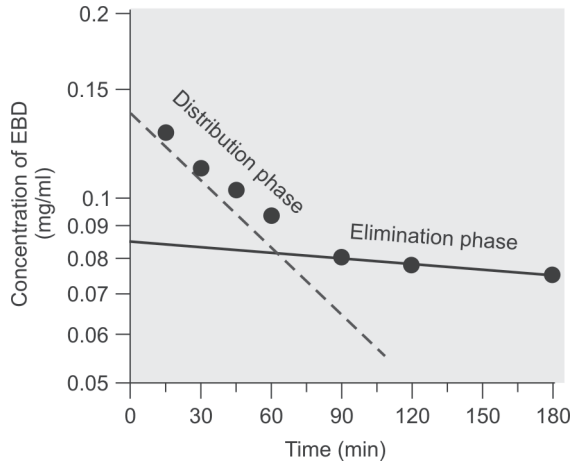

Fig. 2.3: Concentration vs Time Curve

last fraction of the dose disappears irreversibly from the body through metabolism or excretion. For anaesthetic procedures, lasting from a few minutes to a few hours, steady state is never reached. Consequently, the effects related to a dose will change overtime because of this balance but, for most drugs, will be parallel to the concentration at the site of effect.

Understanding the pharmacokinetics (PK) allows clinicians to adjust the delivery scheme in order to control the concentration at the site of effect in the present and in the future (control of recovery). Understanding pharmacodynamics (PD) (that is, the relationship between concentration and intensity of effects) helps in titrating anaesthesia delivery according to individual needs and to successive surgical end-points.

Super-position Principle

Doubling the dose of a drug will double the plasma concentration at anytime, and if two doses are given (e.g. two boluses or bolus + infusion), the plasma concentration will be the sum of the concentrations resulting from each dose. This is linear relationship.

The Concentration vs Time Curve

When we give a single IV bolus of propofol we traditionally start by graphing the plasma concentration versus time. Time is on the X-axis since, it is the independent variable. By convention the very rapid rise in propofol concentration is left out of the graph so that we see only the fall with time. The graph is the sum of negative exponentials, i.e. it is two or more curves added together to form a resultant curve (Fig. 2.3). There should be a distinct elbow in the curve to show the bi-exponential nature, and it has two phases labelled A and B for the redistribution phase and the elimination phase. ("B" is half-life).

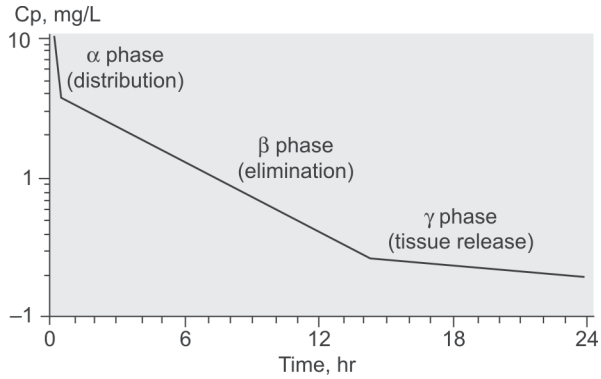

Fig. 2.4

Half-life

The time taken for the plasma concentration of a drug to fall by 50% when first-order kinetics are observed. Many drugs have an initial redistribution phase with a short half-life ($t_{1/2}\alpha$) followed by an elimination phase with a longer half-life ($t_{1/2}\beta$).

Clearance

The apparent volume of plasma from which a drug is entirely removed per unit time. Usually expressed in proportion to bodyweight or surface area (Fig. 2.5).

Volume of Distribution

The volume into which a drug appears to be uniformly distributed at the concentration measured in plasma. Usually a steady state volume of distribution equal to the amount of drug in the body (n) divided by the plasma concentration (C).

The volume of distribution is given by the following equation:

$$\text{Volume of distribution} = \frac{[\text{Amount of drug in the body}]}{[\text{Serum concentration}]}$$