Ion channels, receptors, agonists and antagonists

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Abstract

This article describes the physiology of ion channels and the principal molecular mechanisms responsible for modulating their activity by commonly used drugs in anaesthesia and intensive care. The concept of efficient and selective transport of ions across 'impermeable' plasma membranes is introduced, together with the mechanisms influencing electrochemical signalling within cells. The classification and composition of voltage-gated ion channels are described in the context of their contribution to action potential generation in excitable cells. Drug–receptor interaction of the four main classes of receptor, that is, ligand-gated ion channels (in particular Cys-loop channels), G-protein-coupled, enzyme-linked and nuclear receptors, are described together with an overview of the various signal-transduction mechanisms adopted by metabotropic receptors to control cellular function. Finally, the principles of drug–receptor interaction of agonists, antagonists and inverse agonists are discussed in relation to their affinity, efficacy and potency.

Keywords G-protein-coupled receptors; inverse agonists; ligand-gated ion channels; voltage-gated ion channels

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- describe the range of molecular targets for drugs used in anaesthesia and intensive care
- appreciate the mechanisms underlying their pharmacological effects
- understand basic receptor classification and the principles of drug–receptor interaction

Ion channels

Electrical signalling across lipid membranes is essential for communication within and between cells. However, cell membranes are densely packed phospholipid structures and normally act as impenetrable barriers to permanently charged molecules. To overcome this problem, Nature developed the 'machinery' to selectively transport charged particles across 'electrically-insulated' membranes in order to facilitate the important physiological role of ionic communication. In some cases, ions may be carried across membranes by energy-dependent transporters, but this relatively slow process is limited by the maximal 'turnover' rate of the transporter. A much more rapid and efficient system uses large, membrane-bound glycoproteins, containing water-filled pores (ion channels) together with established electrochemical gradients between the extra- and intracellular compartments. The activation, or gating, of an ion channel results in the rapid, but selective, movement of ions across a plasma membrane. Movement of positively charged ions (cations) into, or negatively charged ions (anions) out of, a cell produces depolarization (or excitation), whereas hyperpolarization (inhibition) of cellular function is brought about by the opposite effect (i.e. movement of negative charges into, or positive charges out of, the cell). The ubiquitous, but diverse nature of ion channels is reflected in the wide range of important biological functions they perform, including cell excitation, muscle contraction and intracellular signalling. In simple terms, ion channels are classified according to the stimulus required to open, or 'gate' the channel. Many different stimuli exist, including neurotransmitters, drugs, alteration of hydrogen ion concentration, temperature and mechanical pressure. However, this review will limit discussion to ion channels activated by neurotransmitters (ligand-gated), or to changes in local membrane potential (voltage-gated).

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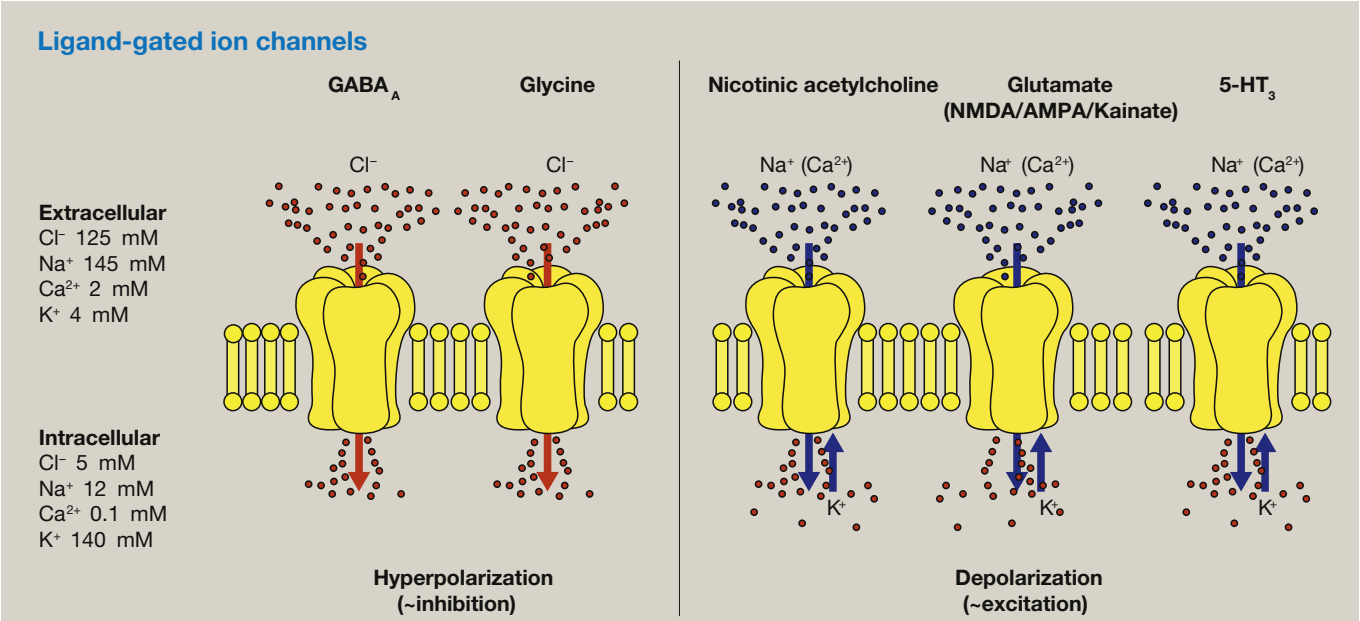
Ligand-gated ion channels

Ligand-gated ion channels are multimeric proteins constructed from large glycoprotein subunits. They are activated by a chemical (agonist) binding to a distinct site or sites within the channel complex. In most cases, neurotransmitters released from presynaptic neurones serve as the primary agonists, acting as part of a complex integrated process required for rapid (millisecond timescale) neuronal communication. Binding of the neurotransmitter to the protein induces a conformational change, resulting in the opening of the integral ion channel. The charge and the direction of ion flux through the activated channel determine its effect on cellular function (i.e. depolarization or hyperpolarization).

Fast excitatory neurotransmission within the central nervous system (CNS) is mediated principally by ionotropic glutamate receptors whereas a superfamily of genetically related ligand-gated ion channels (cysteine loop) is responsible for the majority of fast inhibitory neurotransmission (γ-aminobutyric acid receptor type A ($GABA_A$) and glycine receptors) and, to some extent, excitatory neurotransmission (nicotinic acetylcholine (nACh) and 5-hydroxytryptamine type 3 ($5HT_3$) receptors) (Figure 1). Ionotropic (integrally linked to an ion channel) as opposed to metabotropic (indirectly linked to ion channels via signalling cascade mechanisms) glutamate receptors are important for neuronal excitation and have been implicated in many important physiological and pathological roles including learning, memory and neurodegeneration. Glutamate receptor subtypes are named according to their preferred synthetic agonists (e.g. *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and kainate). Activation of glutamate-gated ion channels initiates the movement of cations (mainly Na^+ and Ca^{2+}) into the cell which results in an



Ligand-gated ion channels (LGICs) mediate the majority of fast neurotransmission within the CNS. Fine tuning of CNS activity is achieved by modulating the activity of inhibitory and excitatory LGICs. Many clinically useful neuroactive drugs alter the activity of LGICs.

5-HT, 5 hydroxytryptamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoazole proprionic acid; $GABA_A$, γ-aminobutyric acid receptor type A; NMDA, N-methyl-D-asparate

Figure 1

excitatory post-synaptic current. If this current has sufficient amplitude, an action potential may be generated. The so-called Cys-loop family of receptors (characterized by a conserved cysteine–cysteine bridge within the extracellular portion of the receptor) mediates a variety of important physiological functions by finely tuning the balance of excitatory and inhibitory activity within the CNS. Most classes of ligand-gated ion channels are susceptible to modulation by drugs used in anaesthesia and intensive care medicine, including general anaesthetics, anxiolytics, anti-emetics and neuromuscular blockers.

Receptor topology: Cys-loop ion channels are composed of five membrane-spanning subunits arranged around a central aqueous pore (Figure 2). Each class of receptor has its own pool of subunits. For example, $GABA_A$ receptors are composed of five subunits taken from a pool of 19 possible subtypes, including α1–6, β1–3, γ1–3, ρ1–3, δ, ε, π and θ. Subunits are constructed from approximately 450 amino acids which fold into a large extracellular domain and four transmembrane domains. The large extracellular domain contains the agonist (e.g. acetylcholine, GABA, glycine) binding site for each channel. The second transmembrane (TM2) domain from each subunit faces into the centre of the protein to line the surface of the aqueous pore or channel. The physicochemical properties (e.g. size and charge) of the amino acids within the TM2 region together with their location within the channel provide the ideal conditions for selectively filtering cations or anions during channel opening. Ionotropic glutamate receptors are composed of four subunits each with three transmembrane domains and a re-entrant loop that contributes to the lining of the channel pore. Glutamate receptor subtypes are drawn from a pool of subunits as follows: NMDA receptors (NR_1, NR_{2A}, NR_{2B}, NR_{2C}, NR_{2D}, NR_{3A} and NR_{3B}); AMPA receptors (A_1–A_4) and kainate receptors (K_5–K_7).

Ligand-gated ion channel modulation: ligand-gated ion channels are susceptible to modulation by many clinically useful classes of drugs. The inhibitory $GABA_A$ receptor is rather promiscuous in this respect because it is sensitive to the modulatory effects of a range of chemically diverse agents, including benzodiazepines, barbiturates and general anaesthetics. The mechanisms underpinning the pharmacology of benzodiazepines have received much attention in recent years. It now seems that some of their clinical effects can be mapped not only to individual subunits, but also to single amino acids within them. Genetically engineered mice harbouring single amino acid mutations within $GABA_A$ receptor subunits are selectively resistant to some of the clinical properties of diazepam. For example, the anxiolytic effects of diazepam appear to be mediated by the α_2-subunit, whereas the sedative effects are mainly mediated by the α_1-subunit. Similar research using intravenous general anaesthetics in mice demonstrates that the sedative and hypnotic effects of etomidate are mediated by β_2- and β_3-subunit-containing $GABA_A$ receptos, respectively. Moreover, it seems that the cardiorespiratory depressant effects of some of the intravenous anaesthetics are also mediated by $GABA_A$ receptors containing β_2- and β_3-subunits.

Voltage-gated ion channels

Voltage-gated ion channels, as their name suggests, are activated by changes to the local membrane potential. Three clinically