Pharmacogenomics and Precision Medicine

Learning Outcomes

- Describe what is meant by the terms ‘pharmacogenetics’, ‘pharmacogenomics’ and ‘personalised/precision medicine’ more generally.
- Discuss generally how knowledge generated from these areas of study might lead to improvements in human/(animal) health.
- Describe how DNA polymorphisms and, in particular, SNPs can lead to changes in protein expression/function.
- Describe, using examples, how SNPs can change the Pharmacokinetic and Pharmacodynamic properties of drugs.
- Be aware of the ethical/economic considerations that the field of Pharmacogenetics/Pharmacogenomics raises.

Introduction to Pharmacogenomics

Pharmacogenomics plays a crucial role in precision medicine, moving away from a one-size-fits-all approach to therapeutics.

- Historically, compounds were modified to suit all patients, but with the understanding of human genome variations, it's clear that individual responses vary.
- Pharmacogenomics aims to identify genetic variations influencing drug efficacy and safety to personalise treatment.

Applications in Cancer Chemotherapy

Cancer chemotherapy has embraced pharmacogenomics for personalised and safer therapies.

- Genetic signatures of patients are used to tailor treatments for better outcomes.

Pharmacogenetics vs. Pharmacogenomics

Pharmacogenetics focuses on polymorphisms of single genes and their influence on drug response, while pharmacogenomics involves broader technology-driven approaches investigating multiple genes and variations.

Importance of Pharmacogenomics

Understanding patient variations in drug responses is crucial due to adverse reactions and lack of efficacy.

- Adverse drug reactions are costly and can be life-threatening, impacting both patients and healthcare systems.
- Lack of drug efficacy in certain patients can delay treatment, especially critical in conditions like cancer.

Impact of Genetic Variations

Polymorphisms in DNA can affect protein activity, drug metabolism, and drug interactions.

- Mutations can be germline or somatic
- Often SNPs
    - Examples of mutations like silent, conservative, and non-conservative mutations can impact protein structure and function.
- Polymorphisms can be direct, altering protein function or binding to drugs, or indirect, affecting gene expression levels.

Detection of Polymorphisms

Advancements in DNA sequencing have made identifying genetic variations more accessible and cost-effective.

- High-throughput DNA sequencing and microarray-based screening help detect single nucleotide polymorphisms linked to drug responses.
- Targeted approaches using chips with nucleotide sequences aid in analysing patient-specific genetic variations.

Pharmacokinetic Aspects

- Genetic polymorphisms in drug-metabolising enzymes can lead to altered drug levels in the body, affecting drug efficacy and adverse reactions.

Pharmacodynamic Aspects

- Proteins like receptors, ion channels, and enzymes can be influenced by genetic variations, impacting drug binding and activity.

Examples of Pharmacogenomics

- Example 1: Drug Metabolism - Suxamethonium metabolism variation due to polymorphic forms of plasma cholinesterase affecting muscle relaxation duration.
- Example 2: Drug Metabolism - Debrisoquine (anti-hypertensive) metabolism by cytochrome P450 enzyme showing varied effects on blood pressure due to enzyme polymorphisms.
- Example 3: Drug Metabolism - Thiopurine methyltransferase enzyme polymorphisms can affect deactivation of 6-mercaptopurine and lead to imbalance of active and inactive drugs, leading to potential adverse effects in leukaemia treatment
- Example 4: Genome-Wide Association Study - Polymorphism in SLC01B carrier protein reducing statin (blood cholesterol reducer) metabolism in the liver, leading to potential muscle damage.

Receptor Polymorphisms in Pharmacogenomics

- Example: Epidermal growth factor receptor (EGFR) polymorphism in lung cancer influences drug choice.
- Example: Enzyme polymorphisms affecting the activity of anticoagulant drug warfarin.
    - Warfarin inhibits clotting factors by targeting the V Corsi enzyme, but polymorphisms in enzymes like CYP2C9 can affect warfarin metabolism, leading to dosing challenges.
    - Individuals with enzyme polymorphisms may require personalised dosing of warfarin to balance clotting prevention and bleeding risks.

Role of Pharmacogenomics in Drug Therapy

- Current prescribing involves trial and error, but pharmacogenomics offers potential for more targeted drug selection.
- Cost and interpretation of genomic data remain challenges in implementing pharmacogenomics in practice.

Ethical and Economic Considerations

Pharmacogenomics raises ethical concerns regarding genetic screening, privacy, and access to tailored therapies based on genetic makeup.

Future of Pharmacogenomics

Pharmacogenomics is advancing precision medicine, but challenges remain in integrating genetic information into clinical practice effectively.

- Pharmaceutical companies are adapting to precision medicine models, focusing on tailored therapies.

Antimicrobial Drugs

Learning Outcomes

- Describe what is meant by the term selective toxicity in regards to antiinfective drugs.
- Describe the mechanism of action of the penicillins and related compounds.
- Identify and discuss other drugs that have antibacterial activity through inhibition of 1) bacterial protein synthesis and 2) bacterial DNA replication.
- Describe bacterial mechanisms of antibiotic resistance.
- Be aware of the clinical dangers associated with resistance to antibiotics and consider ways to avoid/delay this resistance.
- Using the HIV virus as an example, describe key generic points of potential interruption in the viral replication cycle.
- Exemplify this knowledge by describing the mechanisms of action of drugs used to treat infections with HIV, HSV and SARS-CoV2.
- Understand the rationale for combining drugs to treat certain infectious diseases.

Antibiotics

Antibiotics are drugs used to treat infections caused by bacteria. They work through three primary mechanisms of selective toxicity:

- Targeting the bacterial cell wall (e.g., penicillin)
- Inhibition of protein synthesis (e.g., aminoglycosides)
- Inhibition of DNA synthesis (e.g., quinolones)

Drug synergy: combining different antibiotics enhances antibacterial action

Antiviral Drugs

Resistance to antiviral drugs, particularly in HIV therapy, is a significant concern. Understanding viral replication pathways has accelerated the discovery of effective drugs against SARS-CoV-2. The latter part of the lecture focuses on antiviral drugs, with examples including:

- HIV
- Herpes simplex virus
- SARS-CoV-2

Importance of Antimicrobial Drugs

Despite the availability of vaccines, antimicrobial drugs remain essential due to several factors:

- Not everyone can be vaccinated (e.g., immunocompromised individuals)
- Vaccines are not available for all infectious diseases
- Acute infections may require immediate treatment

Selective Toxicity

Selective toxicity refers to the ability of a drug to target pathogens without harming human cells. This concept was pioneered by Paul Ehrlich, who introduced the idea of the "magic bullet"—a drug that selectively kills infectious organisms while leaving healthy cells unharmed.

Understanding the biological differences between pathogens (bacteria, fungi, viruses, parasites) and human cells is essential for developing selective antimicrobial strategies. However, targeting viruses is particularly challenging as they often hijack the host's cellular machinery for replication.

Cancer Treatment Challenges

Targeting cancer cells poses additional challenges since they are derived from the patient's own cells. Cancer therapies often involve drugs that are toxic to both cancerous and healthy cells, leading to a risk-reward scenario where the potential benefits of treatment must be weighed against the side effects.

Evolution of Antibiotics

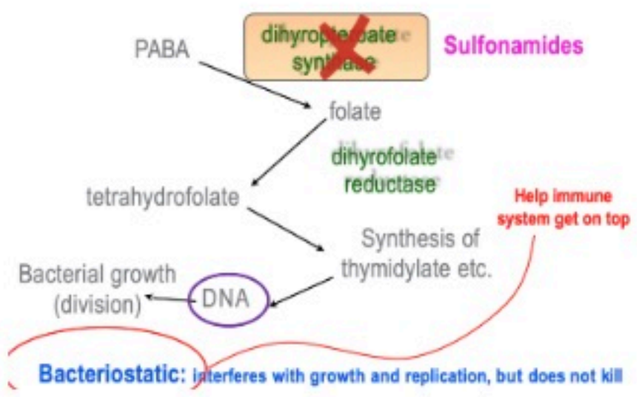
The discovery of antibiotics began with chemical research, leading to the identification of compounds like penicillin in the 1940s. However, the rise of antibiotic resistance has rendered many of these drugs less effective, raising concerns about entering a post-antibiotic era.

Resistance mechanisms have emerged, making it increasingly difficult to treat certain infections. This situation is recognized as a major public health issue, necessitating ongoing research and development of new antibiotics.

Sulfonamides and Mechanism of Action

Sulfonamides are one of the first classes of antibiotics discovered. They inhibit bacterial growth by targeting the folate synthesis pathway, specifically by blocking the enzyme dihydropteroate synthase involved in converting PABA to folate, which is essential for DNA replication.

While sulfonamides are bacteriostatic (they inhibit growth rather than kill bacteria), they allow the immune system time to eliminate the infection. However, some bacteria are inherently resistant to sulfonamides, leading to the development of combination therapies.



Combination Therapy: Trimethoprim and Sulfonamides

Trimethoprim is another antibiotic that targets the dihydrofolate reductase enzyme in the folate synthesis pathway. When used in combination with sulfonamides, it enhances antibacterial efficacy through synergistic action. This dual targeting is effective against certain bacterial strains. Importantly, while both drugs target similar pathways, they exhibit selective activity towards bacterial enzymes over human enzymes, minimising toxicity to human cells.

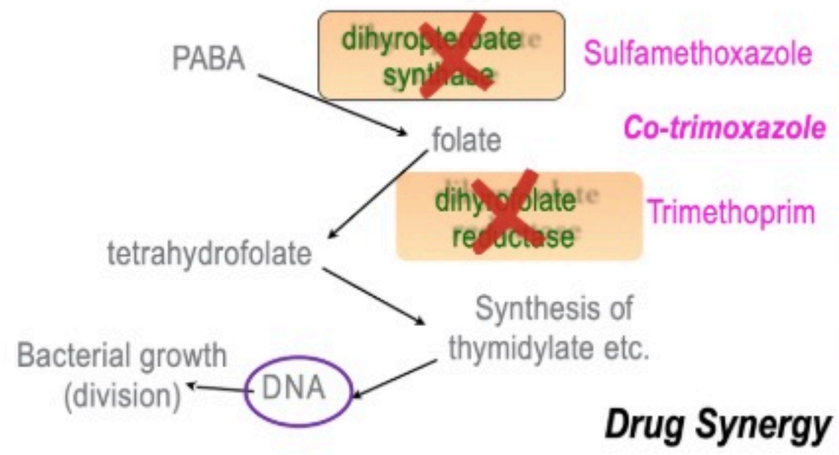


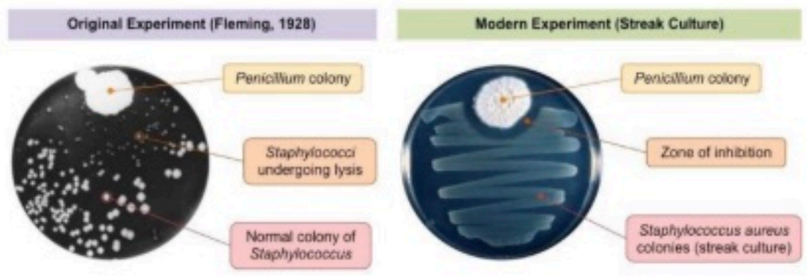
Table 44.1 Specificity of inhibitors of dihydrofolate reductase

Inhibitor	IC_{50} (μmol/l) for dihydrofolate reductase		
	Human	Protozoal	Bacterial
Trimethoprim	260	0.07	0.005
Pyrimethamine	0.7	0.0005	2.5
Methotrexate	0.001	~0.1[a]	Inactive

[a]Tested on *Plasmodium berghei*, a rodent malaria.

Introduction to Penicillin

Penicillin is one of the most famous antibiotics, discovered by Alexander Fleming in London. The discovery stemmed from an experiment where a forgotten culture plate revealed that a fungus was killing off bacterial colonies. This led to the identification of penicillin as a potent antibiotic, earning Fleming and his collaborators a Nobel Prize.



Initial Challenges with Penicillin

Despite its effectiveness, penicillin faced challenges, including bacterial resistance and a short half-life in the body. The first patient treated with penicillin, a policeman suffering from sepsis due to a rose bush injury, did not receive enough of the drug to save him. Efforts to re-isolate the drug from his urine were unsuccessful, highlighting the need for more stable penicillin variants.

Mechanism of Action

Penicillin and its derivatives work by targeting the bacterial cell wall, which is composed of peptidoglycan—a structure made of sugars and peptides that provides rigidity and integrity. The enzyme transpeptidase is crucial for forming cross-bridges in the peptidoglycan layer. Penicillin inhibits this enzyme, leading to weakened cell walls that cannot withstand internal pressure, causing bacterial cells to burst during division.

Selective Action of Penicillin

Penicillin is selective for bacterial cells because human cells do not have cell walls or the transpeptidase enzyme. This selectivity minimises harm to human cells while effectively targeting bacteria.

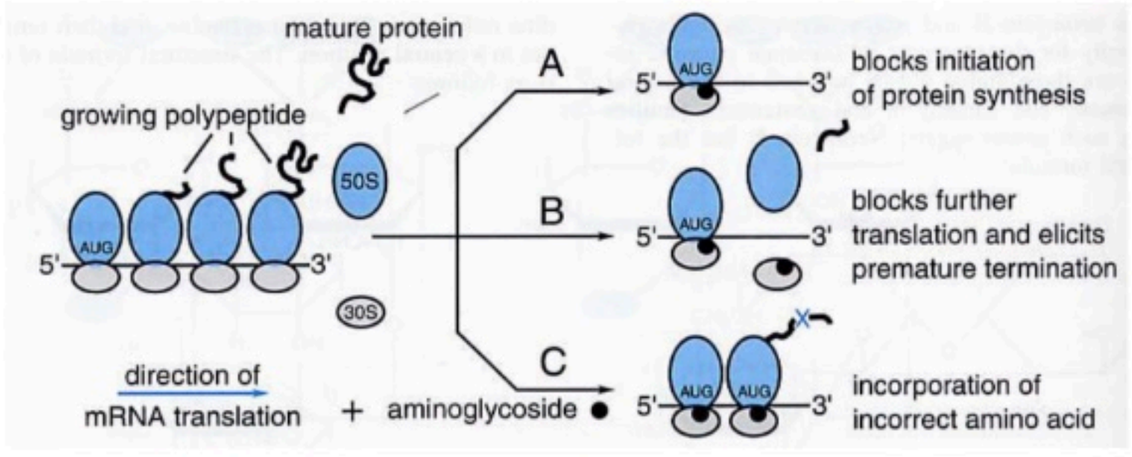
Adverse Effects of Penicillin

- Disruption of the microbiome, potentially leading to gastrointestinal issues.
- Hypersensitivity reactions, including anaphylaxis in sensitive individuals.

These adverse effects can arise from the targeting of both harmful and beneficial bacteria, leading to a range of health issues.

Other Antibiotic Mechanisms

In addition to beta-lactam antibiotics like penicillin, other classes of antibiotics target different bacterial functions. One such class is aminoglycosides, which inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit. This binding can disrupt the initiation of protein synthesis, lead to truncated proteins, or incorporate false amino acids, ultimately resulting in bactericidal effects.



Synergistic Effects in Antibiotic Therapy

In cases of difficult-to-treat bacterial infections, combination therapy may be employed. For example, using a beta-lactam antibiotic alongside an aminoglycoside can enhance the effectiveness of treatment. The beta-lactam antibiotic weakens the bacterial cell wall, allowing better penetration of the aminoglycoside, which then inhibits protein synthesis more effectively.

Quinolones and Other Antibiotics

Quinolones, such as ciprofloxacin, represent another class of antibiotics that inhibit bacterial DNA replication. They target the enzyme DNA gyrase, which usually unwinds the bacterial genome for duplication. Other antibiotics may also interfere with folic acid synthesis or target cell wall integrity.

Introduction to Antibiotic Resistance

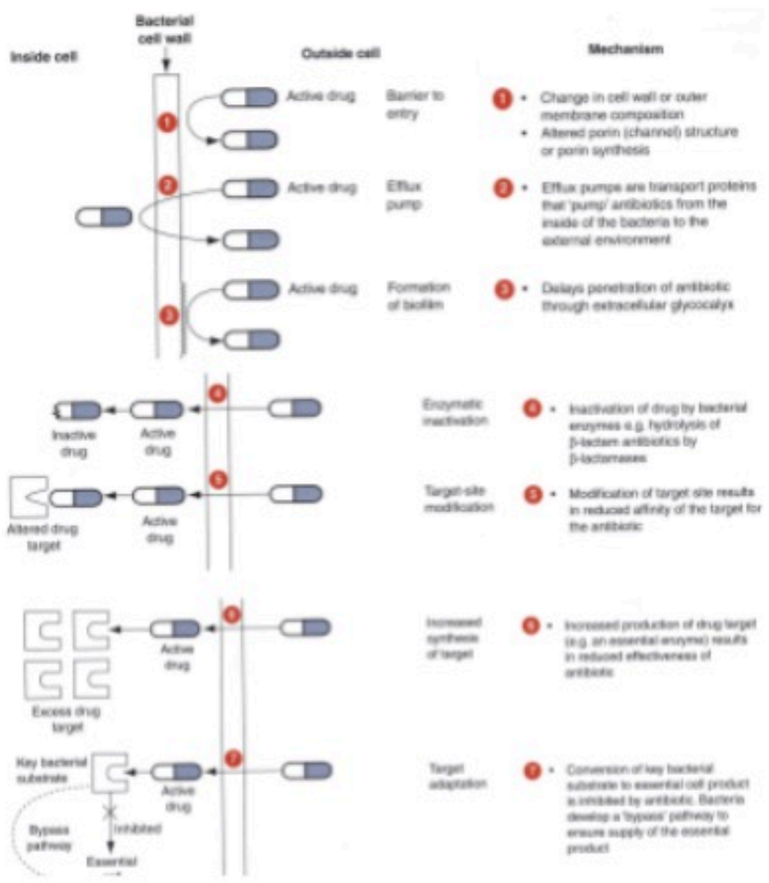
Antibiotic resistance is a significant and growing problem in modern medicine. It arises when bacteria evolve mechanisms to resist the effects of antibiotics, rendering these life-saving drugs ineffective. This phenomenon poses serious challenges for treatment and public health.

Shortly after the introduction of penicillin, it became evident that some bacteria had developed resistance. This resistance is a result of evolutionary processes where random mutations provide certain bacteria with survival advantages when exposed to antibiotics.

Mechanisms of Resistance

Bacteria have evolved various mechanisms to resist antibiotics, including:

- **Enzymatic Breakdown:** Bacteria can produce enzymes, such as beta-lactamase, which cleave the beta-lactam ring of penicillin, rendering it ineffective.
    - Can be inhibited by β-lactamase inhibitors e.g. clavulanic acid
- **Altered Binding Sites:** Some bacteria change their cell wall features, making it difficult for antibiotics to bind effectively.
- **Efflux Pumps:** Bacteria can develop pumps that actively expel antibiotics from their cells.
- **Biofilm Formation:** Certain microorganisms form biofilms that create a protective barrier against antibiotic penetration.
- **Target Modification:** Bacteria may mutate the target sites of antibiotics, reducing their sensitivity to inhibition.
- **Overproduction of Targets:** Bacteria can increase the production of the target molecules that antibiotics aim to inhibit.
- **Alternative Pathways:** Bacteria may develop alternative metabolic pathways that bypass the inhibited pathways targeted by antibiotics.



Pharmacology of the CNS

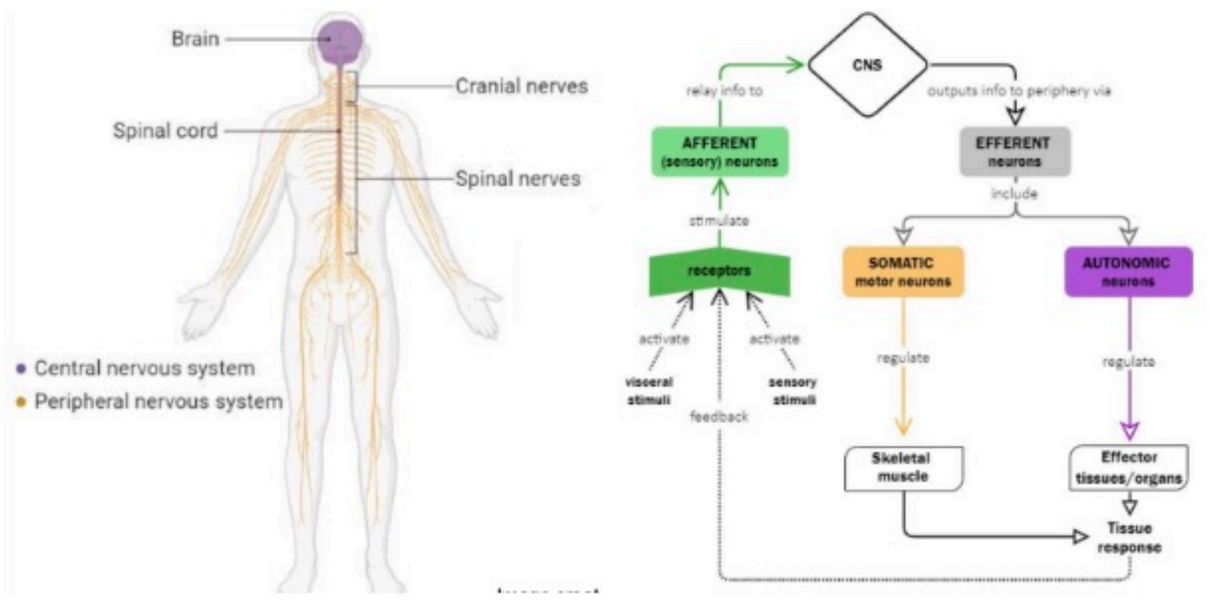
Introduction to CNS Pharmacology

Learning Outcomes

- Describe major components of the central nervous system and features of neurones
- Explain the similarities and differences between neurotransmission in the peripheral nervous system and central nervous system (CNS)
- Discuss the GABA A receptor and how it is modulated
- Describe, using examples, the major sites where drugs act to modulate synaptic neurotransmission in the CNS
- Appreciate the importance of the blood-brain barrier

Neuronal Structure and Function

Neurons can transmit signals over long distances, with some projections reaching significant lengths.



Neuronal Count and Synaptic Connections

There are approximately 100 billion neurons in the human brain, forming around 1000 billion synapses. This vast network creates a highly complex system that researchers are still striving to fully understand.

Historical Perspectives on Neuronal Function

The study of neuronal function has evolved over centuries. Luigi Galvani, an Italian anatomist, contributed to early theories about the electrical nature of nerves through experiments with frog legs. His work laid the groundwork for understanding nerve function as electrical transmission.

Advancements in Neuroscience

With the advent of electron microscopy in the mid-20th century, scientists discovered the synaptic gap between neurons, leading to the hypothesis of chemical transmission. John Eccles, an Australian scientist, recorded action potentials and proposed that neurotransmitter release occurs in discrete packets (vesicles), marking a significant advancement in our understanding of neuronal communication.

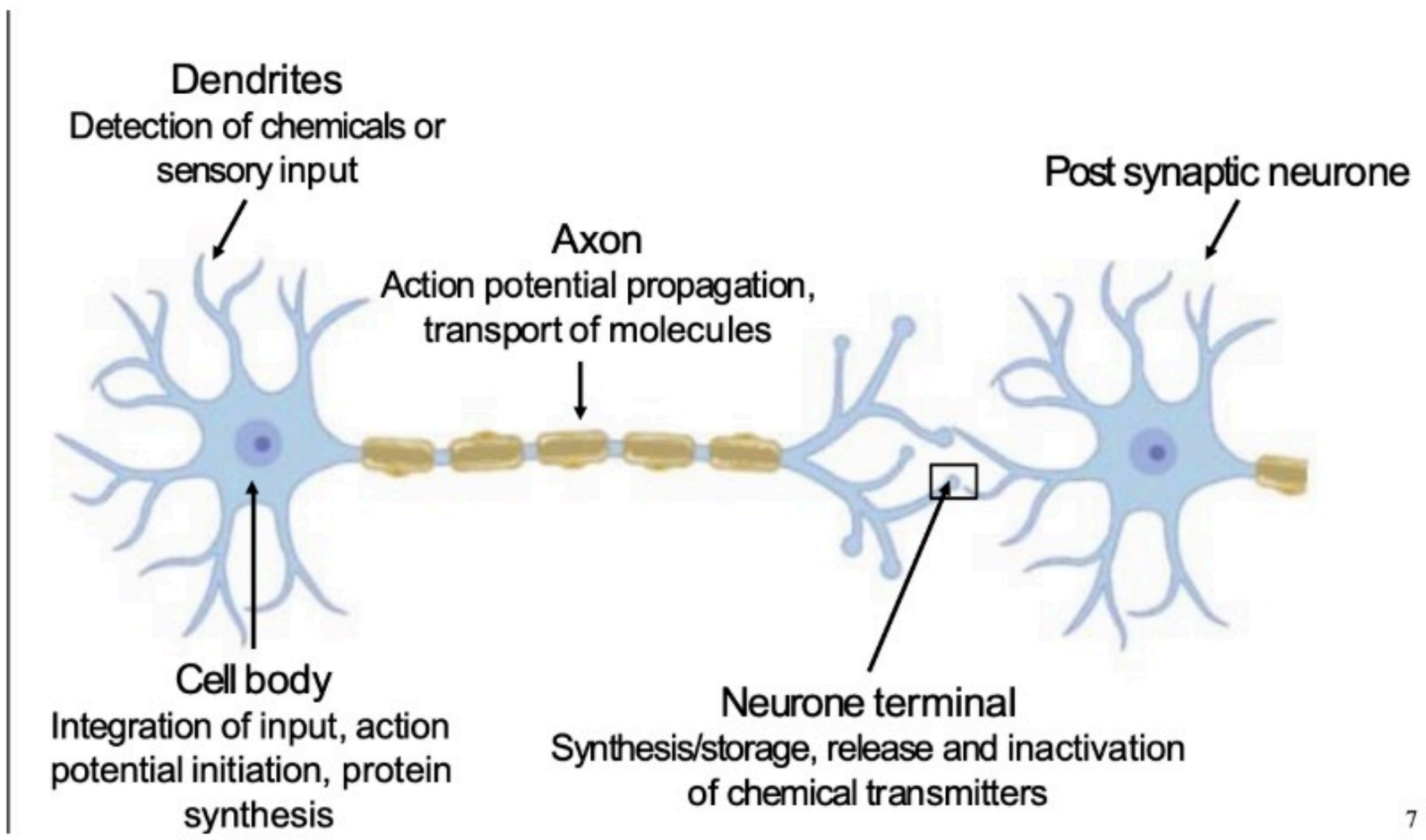
Neurons Overview

Neurons are classified into presynaptic and postsynaptic neurons, with the presynaptic neuron synapsing with the postsynaptic neuron. The action potential travels down the myelin sheath, leading to the fusion of vesicles and the release of neurotransmitters that alter the state of the postsynaptic neuron.

Neurotransmitter Synthesis and Release

Dendrites are responsible for detection of chemicals or sensory input. The cell body of a neuron is responsible for integration of input and synthesising neurotransmitters, which are then transported along the axon to the nerve terminal. Some neurotransmitters are synthesised and packaged at the terminal, depending on the type of neurotransmitter. The processes of synthesis, storage, release, and inactivation are crucial for neurotransmitter modulation.

- **Synthesis:** Creation of neurotransmitters in the cell body.
- **Storage:** Packaging of neurotransmitters in vesicles.
- **Release:** Fusion of vesicles with the membrane to release neurotransmitters.
- **Inactivation:** Mechanisms to deactivate neurotransmitters after their action.



Synaptic Complexity

- Neurons can receive multiple synaptic inputs, with many synapses influencing their activation or inhibition.
- In the neuromuscular junction, one motor neuron can synapse with hundreds of muscle fibres, leading to a clear action potential and muscle contraction.
- In contrast, central nervous system (CNS) neurons can synapse with thousands of other neurons, resulting in more complex interactions
    - Action potentials lead to small change in in membrane potential of postsynaptic neuron

Neurotransmitter Types

- Different neurotransmitters can have excitatory or inhibitory effects.
- Acetylcholine is the primary neurotransmitter of neuromuscular junctions and is exclusively excitatory.
- At the CNS synapse, several neurotransmitters are stored in the presynaptic neuron, several neurotransmitters can be released from CNS synapse, and neurotransmitters can be excitatory OR inhibitory. The complexity of neurotransmitter interactions is illustrated by the variety of neurotransmitters present in the brain.

Neurotransmitters released in the CNS

Acetylcholine

Amines

Noradrenaline
Adrenaline
Dopamine

Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrine

Serotonin (5-HT)

Histamine

Amino Acids

GABA
Glycine
Glutamate

Peptides

LH
ACTH
ADH
Substance P
VIP
Insulin
Angiotensin II
Neuropeptide Y
Somatostatin
Endorphin
Oxytocin
Cholecystokinin (CCK)
Neurotensin
Glucagon

Novel

Nitric Oxide (gas)
Carbon Monoxide (gas)
ATP

Receptor Diversity

Neurotransmitter receptors are diverse, with multiple types for each neurotransmitter. For example, acetylcholine binds to muscarinic and nicotinic receptors, each with distinct functions.

Acetylcholine:
- Muscarinic: M1, M2, M3, M4, M5
- Nicotinic: N1, N2, N3, N4, N5, N6, N7, N8, N9, N10

Noradrenaline: / Adrenaline: $\alpha1$, $\alpha2$, $\alpha3$, $\beta1$, $\beta2$, $\beta3$

Dopamine: D1, D2, D3, D4, D5

Serotonin: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{3}, 5-HT_{4}, 5-HT_{5A}, 5-HT_{5B}, 5-HT_{6}, 5-HT_{7}

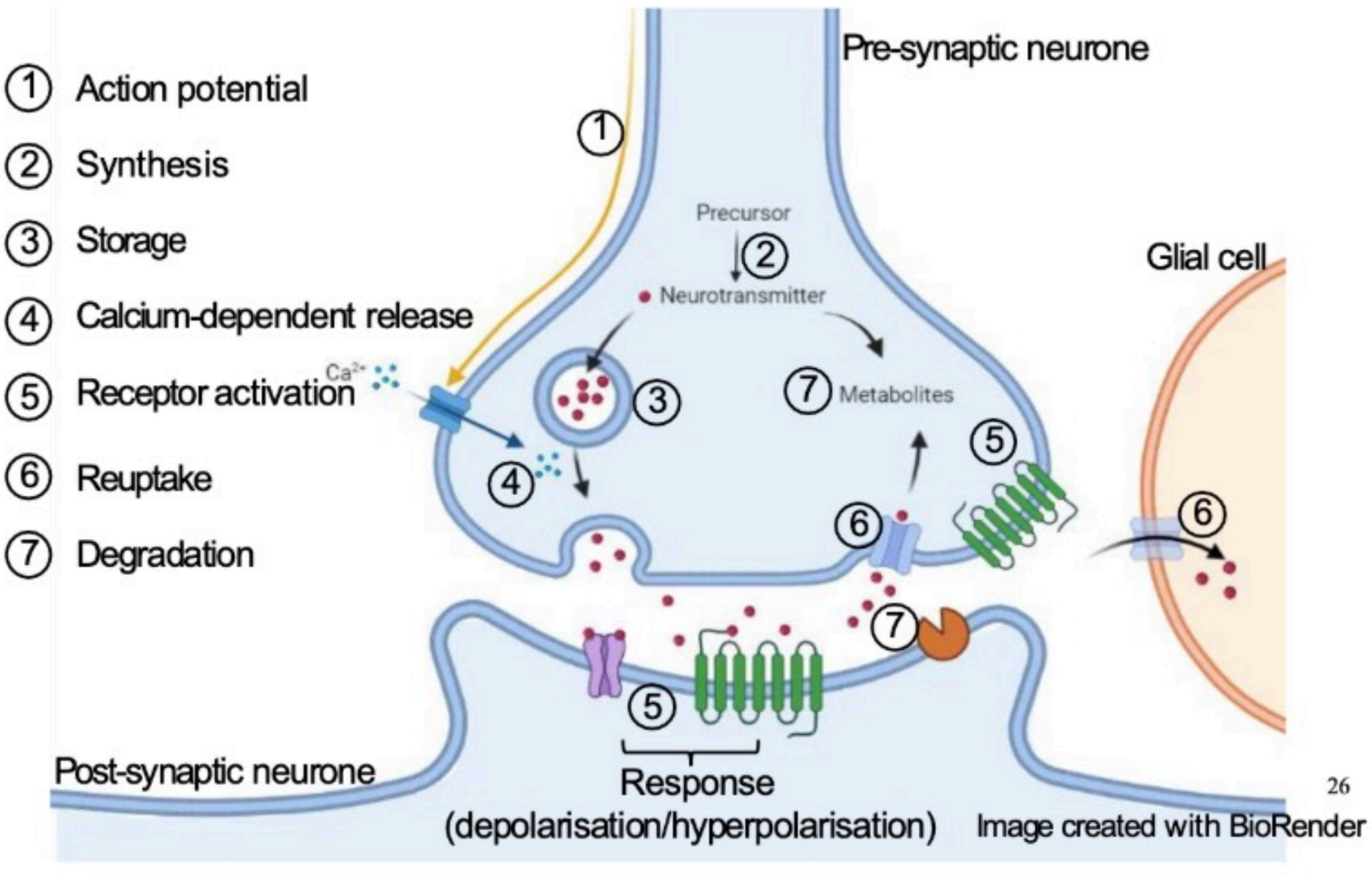
GABA: $GABA_A$, $GABA_B$

Excitation and Inhibition

Synapses can be either excitatory or inhibitory, but not both simultaneously. Excitatory neurotransmitters like acetylcholine increase the likelihood of action potentials, while inhibitory neurotransmitters like glycine decrease it. Some neurotransmitters, such as serotonin and dopamine, can have either effect based on the receptor they interact with.

Introduction to Neuropharmacology

Understanding neuropharmacology is crucial for grasping how drugs affect the central nervous system (CNS). Key concepts include how drugs influence action potentials, synthesis, storage, release, receptor activation, reuptake, and degradation of neurotransmitters.



Drug Action Mechanisms

Ehrlich proposed that drugs exert their effects by binding to specific targets such as receptors, ion channels, carrier molecules, enzymes, or DNA. This binding is essential for drug action.

- **Agonists:** Activate receptors by binding to neurotransmitter sites.
- **Antagonists:** Block receptor activation.
- **Allosteric Modulators:** Bind to different sites, altering receptor conformation and affecting neurotransmitter binding.

Neuronal Development and Neurotrophic Factors

- Neurotrophic factors:
    - Chemicals released from supporting cells
    - Nerve development
    - Maintain nerve integrity/function
    - Tyrosine kinase receptors
- Neurodegenerative diseases
    - toxic insult: oxidative stress
    - loss of nerves/nerve function
    - loss of neuroprotective factors
- Blood brain barriers
    - Limit entry of molecules into the brain
    - Physical & chemical: endothelial tight junctions in capillaries of the cerebral circulation and efflux transporters

Glutamate and GABA

Glutamate is an excitatory neurotransmitter, while GABA is inhibitory. Their mechanisms include:

- **Glutamate:** Causes sodium influx, changing resting potential and facilitating action potential propagation.
- **GABA:** Induces chloride influx and potassium efflux, raising the threshold for action potential generation.