Module Code: BIO00046I

Examination Candidate Number: __________
Desk Number: __________

BSc Degree Examinations 2018-9

Department:
BIOLOGY

Title of Exam:
Pharmacology

Time Allowed:
1.5 hours

Marking Scheme:
Total marks available for this paper: 60
Section A contains interpretation and data handling questions (40 marks). Section B contains an essay question (one from 2 choices) 20 marks

Instructions:
Answer all questions in Section A and question in Section B.

Materials Supplied:
CALCULATOR and Graph Paper

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DO NOT TURN OVER THIS PAGE UNTIL INSTRUCTED TO DO SO BY AN INVIGILATOR
SECTION A:

Answer all questions in the spaces provided.

Mark total for this section: 40

1.

a) Describe how the route of drug administration may be tailored to the specific needs of the patient giving examples of relevant clinical situations in each case.

(3 marks)

Absorption, Distribution, Metabolism, Excretion. Oral route OK for slow release, non-emergency situations. Situations where liver function and swallowing is not compromised. IP/IM for drugs that do not survive the gut/1st pass (eg. Insulin). IV for rapid effects, eg. Acute pain relief, immediate intervention for systemic infection. Rectal (direct access to alimentary system, use when swallowing compromised (Macy catheter). Topical for skin complaints. Depot for slow release. 1 mark for any of the above.

b) If a patient inadvertently overdoses on a drug what clinical interventions are available to minimise resulting harm?

(2 marks)

Gastric lavage. Induction of vomiting. pH change to increase metabolism and excretion (e.g. Aspirin given in lectures - urine). Administration of antagonists. Clinical intervention to support affected tissues/organs. 1 mark for any of the above.

2.

a) Once a drug is present in the target tissue what factors determine the time course of the drug’s action?

(3 marks)

Any 3 (1 mark each) from: Type of receptor/effector system. Rate of desensitisation of the receptor molecule. Local metabolism. Rate of new protein production/old protein elimination for nuclear receptors. Lifetime of the Drug-receptor complex. Oppositional tolerance.

b) Explain why this may be important for achieving the desired therapeutic effect.

(2 marks)

Any 2 from: Timecourse needs to match dosing regime (therapeutic window). Administration needs to avoid dependence. Care needed to avoid build-up of drug and manifestation of unwanted side-effects.
3. For drugs acting at G protein-coupled receptors:

a) Give an example of a drug-receptor-effector pathway for a drug acting via Gas (G protein subunit alpha-S) (3 marks)

Example worked through in the course: Insulin, Insulin receptor, Adenlylyl cyclase/PKA, Lipase and/or Glycogen synthase, phosphorylase. 1 mark for receptor/ligand. 1 mark for 2nd messenger enzyme. 1 mark for target enzyme(s).

b) Give an example of drug-receptor-effector pathway for a drug acting via Gaq (G protein subunit alpha-q) (3 marks)

Example worked through in the course: Acetylcholine, M1 AchR, LPC, IP3/DAG leading to PKC activation, calcium release from stores (IP3R, SERCA). 1 mark for receptor/ligand. 1 mark for 2nd messenger enzyme. 1 mark for target enzyme(s).

4. If a receptor changes calcium ion concentration inside a cell ([Ca^{2+}]):

a) Briefly explain three possible consequences in terms of change in cell function. (3 marks)

Any 3 of the following: Synaptic plasticity, membrane excitability, Exocytosis, Motility, structural cell changes, contraction, differentiation, mitosis/meiosis, apoptosis (3 marks).

b) Calcium ion concentration can increase in the cytoplasm owing to influx through L-type calcium channels or by release from intracellular stores. Which drugs affect these systems and what may they be useful for clinically? (2 marks)

L-channels: Dihydropyridines (eg. Amlodipone) or Benzothiazepines (eg.g verapamil), Stores: caffeine, thapsigargin (1 mark for an eg for BOTH sources). Altering blood pressure, adjusting cardiac output/heart rhythm and rate (1 mark).
5. Below is the change in plasma concentration ($C_p$) of two newly developed chemotherapeutic drugs immediately following an intravenous bolus dose.

![Graph showing plasma concentration over time for Drug A and Drug B.](image)

a) Which compartment model best describes the pharmacokinetic profiles of these drugs and why? (2 marks)

The single compartment model (1 mark) because drug is eliminated via a single exponential decay (straight line on log scale) (1 mark).

b) What is the value of $C_0$ for each drug? (1 mark)

Drug A: 40 µmol/l (1/2 mark). Drug B: 100 µmol/l (1/2 mark).

c) What is the elimination rate constant ($K_{el}$) for each drug? Show how you arrived at your answer. (4 marks)

$K_{el} = \text{inverse of the slope when } C_t \text{ is plotted on a log scale.}$

Drug A: $36/50 = 0.72 \text{ h}^{-1}$ (2 marks).
Drug B = 99/30 = 3.3 h⁻¹ (2 marks).

6. In a study examining the effects of a potential new treatment for anxiety the drug (X) is tested in an assay quantifying the effects of the stress hormone cortisol on plasma noradrenaline (NA) levels. The following values were obtained:

<table>
<thead>
<tr>
<th>Cortisol conc’n (mM)</th>
<th>[NA] (nM) (cortisol alone)</th>
<th>[NA] (nM) (cortisol + Drug X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.002</td>
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<td>76</td>
</tr>
<tr>
<td>0.010</td>
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<td>167</td>
</tr>
<tr>
<td>0.020</td>
<td>327</td>
<td>204</td>
</tr>
<tr>
<td>0.050</td>
<td>430</td>
<td>250</td>
</tr>
<tr>
<td>0.100</td>
<td>456</td>
<td>255</td>
</tr>
</tbody>
</table>

a) Plot a concentration-response curve (semilog) of the effects of cortisol alone and cortisol plus drug X. Label axes appropriately. (3 marks)

Marks for correct curve shapes, x-axis labels (log) and y-axis labels.

b) What are the approximate binding affinities ($K_d$) for cortisol alone and in the presence of drug X. (2 marks)
Cortisol alone = 0.011-0.015 mM, +drug X = 0.007-0.009 mM. Must have units.

c) What type of agonist or antagonist best describes drug X for this effect of cortisol. Explain your answer. (1 mark)

Non-competitive antagonist. Efficacy reduced.

7. Consider the following 2 brief case studies:

a) A 60 year old woman who has previously been prescribed codeine for pain relief for her headaches visits her GP to complain that she is feeling no better. Provide a pharmacological explanation for why this may be the case. (3 marks)

Codeine is activated to morphine which has the analgesic effect (1 mark). This activation is carried out by CYPD26/cytochrome P4502D6 which displays genetic variation (1 mark). The woman may be a poor metaboliser and therefore doesn’t metabolise the codeine to morphine effectively to produce the analgesic effect (1 mark).

b) A 24 year old student from Thailand starts to develop nausea, as well as a red flush and eventually suffers from vomiting after drinking champagne at their graduation ceremony. Provide a pharmacological explanation for their symptoms. (3 marks)

Alcohol is metabolised by acetaldehyde hydrogenase (ALDH1/2) (1 mark). Up to 50% of the Asian population have low activity of aldh2 -(1 mark). Student is a homozygote for ALDH2*2 which means can't detoxify the alcohol and gets a build up of acetaldehyde which causes the symptoms (1 mark)
SECTION B: Essay question

Answer one question from this section.

Mark total for this section: 20

A. Describe the main types of adverse drug reaction (ADR) seen in the clinic. Briefly explain the cause(s) of each.

Or

B. Compare and contrast the four main receptor-effector systems used by drugs to alter biological processes.

Model answer A.

Intro – up to 2 marks for putting the question in context.

ADRs common. Up to 10% of A&E cases related to drug toxicity.

Types of adverse drug reaction seen:

Related to primary pharmacological property (up to 5 marks)


Unrelated to primary pharmacological property (up to 5 marks)


Expand on DNA covalent bonding (up to 3 marks)

Correlates with risk of mutagenesis/carcinogenesis. Only one mutation required. If it is in a proto-oncogene or endogenous tumour suppressing transcription factors = cancer. Subclassification of carcinogenic properties (IARC groups 1-4). Tested for new drugs using animal models and cell culture models. Use examples related to hepatocellular carcinogenesis. General examples of common carcinogens (not all drugs).
Expand on teratogenesis (up to 2 marks)


Anaphylaxis (up to 3 marks).

Drug – protein interactions (hapten). Stable conjugate not recognised by the endogenous immune system, therefore immune response elicited. Symptoms/severity depends on the the drug-protein conjugate produced, its location and the type of immune response generated. Examples: IgE: Fast atopic reaction, asthma, anaphylaxis, shock. IgG, IgM: haemolytic anaemia. IgG: Serum sickness (fever, joint pain, nephrotoxicity). T-cells: Contact dermatitis. Severe reactions can be deadly, Brocospasm, oesophageal inflammation cause respiratory failure. Excessive fluid accumulation in tissues leads to hypotension and can lead to circulatory failure.

Model answer B.

Intro – up to 2 marks.

4 main receptor subtypes (ion channels, GPCRs, kinase-linked receptors, nuclear receptors). 4 main effector systems (membrane conductance, second messenger system activation, kinase activation leading to protein phosphorylation chances), transcription factor activation/suppression changes protein complement of cells.

Ion channels. (5 marks)

Effect is fast and transient. Drug reaches receptor directly via interstitial fluid or cell membrane. Receptor is a protein complex (4-5 transmembrane proteins) forming a pore or channel that allows ions to flow into and out of a cell – controls cell excitability (heart, muscle, brain) and indirectly second messenger systems via calcium ion entry. Pore can be normally closed (no constitutive activity, eg. Sodium channel) or open (constitutively active, eg. 2-pore potassium channels controlling resting membrane potential). Drug binding alters the quaternary structure of the protein complex and can thus open/close the channel, change its activation/inactivation or alter its membrane potential dependence through phosphorylation changes (compare with GPCRs and kinase-linked Rs). Example – use Na channel. Open channel block from extracellular side (e.g. tetrodotoxin), open channel block from intracellular side (e.g. local anesthetics, some anti-epileptic drugs), alter pore kinetics (change activation, eg. Veratridine), Change phosphorylation state (eg via GPCRs).

GPCRs (5 marks)

Effect is intermediate fast-slow. Drug receptor is on cell membrane as for ion channels. Drug reaches binding site via extracellular fluid. Receptor is a single protein with 7 transmembrane segments. No pore is produced so no direct effects on cell excitability. Instead, agonist binding causes catalytic cleavage of intracellular G-protein into the alpha subunit and beta/gamma subunit. The alpha subunit is an active GTPase though which all subsequent effects are produced. If GTP is hydrolysed by active alpha subunit the G-protein reforms into the alpha/beta/gamma complex and rebinds to the inactive receptor protein. The G-protein is embedded in the intracellular leaflet of the cell membrane so effects limited to membrane-bound enzymes or ion channels.
Different G-protein subtypes confer multiple effector responses. Ga\(_{\text{S}}\) coupled to receptors for many neuromodulators (noradrenaline, histamine, serotonin). Couple directly to adenylyl cyclase increasing cAMP levels. This can then activate protein kinases (PKA) to change enzyme activity. Use beta-adrenoceptor and glycogen pathway utilisation to increase cell energy. Ga\(_{\text{I/O}}\) couple receptors for endocannabinoids, immune modulators, opiates. Have the opposite effect cf Ga\(_{\text{S}}\) in that they inhibit adenylyl cyclase thus decrease cAMP levels. Ga\(_{\text{Q}}\) couples receptors from cholinergiuc drugs, prostaglandins, stress and sex steroids. Activate phospholipase C NOT Adenyly cyclase. Increase DAG and IP\(_3\) levels. Use example of the M1 muscarinic receptor to explain this pathway. Link the pathway to control of intracellular calcium and further second messenger system activations. Expand to show convergence and divergence of GPCR-receptor mediated effects.

**Kinase-linked receptors (5 marks)**

Slow mainly metabotropic effects. Again, cell membrane-incorporated proteins. Single protein spans the membrane. Binding of drug to the extracellular side causes dimerization. Dimerisation cases autophosphorylation of tyrosine residues and activates a catalytic site for SH2 domains of a variety of intracellular proteins. 2 examples: RAS/Raf/MAP kinase pathway. Ras=membrane bound protein, hydrolyses GTP to become active. Phosphorylates Raf – phosphorylates Mek, phosphorylates MAP kinase to activate various transcription factors and control gene transcription. Jak/Stat pathway. 2 x Jak proteins phosphorylated – phosphorylate 2 x Stat which then alters gene transcription. Work along side GPCRs via phosphorylation pathways to activate multiple kinase cascades and control almost all facets of cell function (e.g. physiological responses, immune responses, cell death, cancer/growth/differentiation.

**Nuclear receptors (3 marks)**

Very slow, found in cytoplasm and in nucleus therefore drugs have to be able to cross the cell membrane to reach their binding site. 48 different types responding to hormones and directly altering gene transcription. Cytoplasmic NRs are homodimers. Nuclear NRs are heterodimers with retinoid receptor. Specifically bind to hormone response elements on DNA promoter sequences recruiting co-activators and co-repressors. Eg. Sex steroids (oral contraceptives). NB. Responses indirectly affect pharmacokinetics of most prescription drugs, therefore care needed with co-administration.