UNIVERSITY OF YORK
BSc Stage 2 Degree Examinations 2017-18

Department:
BIOLOGY

Title of Exam:
Pharmacology

Time allowed: 1 hour and 30 minutes
Total marks available for this paper: 80

This paper has three parts:

Section A: Short answer questions (30 marks)
- Answer all questions in the spaces provided on the examination paper

Section B: Problem questions (20 marks)
- Answer all questions in the spaces provided on the examination paper

Section C: Long answer question (marked out of 100, weighted 30 marks)
- Answer either question A or question B
- Write your answer on the separate paper provided and attach it to the back of the question paper using the treasury tag provided
- The marks available for each question are indicated on the paper
- A calculator will be provided

For marker use only:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total as %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DO NOT WRITE ON THIS BOOKLET BEFORE THE EXAM BEGINS
DO NOT TURN OVER THIS PAGE UNTIL INSTRUCTED TO DO SO BY AN INVIGILATOR
SECTION A: Short answer questions

Answer all questions in the spaces provided

Mark total for this section: 30

1. a) Which organ is involved in the "first pass" metabolism? (1 mark).
   Answer: Liver (1 mark)

b) Name two common systemic drug administration routes aimed at avoiding the "first pass" metabolism. (2 marks).
   Answer: 2 from the following (1 mark each), intravenous (i.v.), intramuscular (i.m.), intradermal (i.d.), subcutaneous (s.c.) injections, sublingual (s.l.) and rectal administrations.

c) Name two phase 2 chemical reactions involved in first pass drug metabolism. (2 marks).
   Answer: Any 2 (1 mark each) from - glucuronidation, sulfoconjugation, amino acid conjugation.

2.

Describe the two main types and features of adverse drug reactions to medicinal products and briefly explain the differences. (6 marks)

Answer: Type A= Augmented adverse reactions (1 mark). Any two of the following (1 mark each): Related to dose and susceptibility; Often dose dependent; May be reversed by dose reduction; Drug toxicity may be due to synergistic effect with a co-administered drug; ADR unrelated to pharmacological property = to drug’s principal mode of action. Type B= bizarre reaction (1 mark). Any two of the following (1 mark each): Side-effects more difficult to predict; Idiosyncratic- cause often unknown; Could be due to an enzyme inhibition/activation; A genetic deficiency of an enzyme; An active metabolite.
3. 

a) Give an example of drug-enzyme interactions which first led clinicians into the field of pharmacogenetics. Name both the enzyme and drug involved. (2 marks).

Answer: One of the following 3 pairs (1 mark for enzyme, one for drug):
glucose-6-dehydrogenase deficiency and primaquine;
acetylation/N-acetyltransferase 2 and isoniazid; atypical plasma cholinesterase and succinylcholine.

b) Give an example in childhood leukaemia where pharmacogenetics is important. Name the pathway/enzyme and drug involved. (2 marks)

Answer: examples given include: folate pathway or MTHFR (1 mark), methotrexate; thiopurine methyltransferase (1 mark) 6-mercaptopurine (1 mark).

c) Give two examples of the potential benefits of considering pharmacogenetic or pharmacogenomic data. (2 marks)

Answer: examples given include: improved drug choice (1 mark); reduction in side effects/toxicity (1 mark), correct dose administered/improved therapeutic effect (1 mark); reduction in health care costs (1 mark); personalised medicine (1 mark); reduction in hospital admissions for ADR’s; pre-screening tools (1 mark).

4. 

a) Give 3 reasons why drug effects mediated by GPCRs are so diverse (3 marks).


b) Give an example of a drug-receptor-effector-enzyme target combination for a G-protein-coupled receptor system targeted by mood stabilising drugs such as lithium. (3 marks)

Example worked through in the course: Acetylcholine, M1 AchR via $G_\alpha q$ (1 mark), LPC, IP3/DAG leading to PKC activation, calcium release from stores (IP3R, SERCA) (2 marks).
5. a) Describe three adverse consequences of using drugs with strong bonds (e.g. Ionic, hydrophobic, covalent) to their receptor targets. (3 marks)

Answer: Problems with administration (1 mark). Covalent bonds are permanent. The drug effect will not decay until new receptors are made (1 mark). High AFFINITY of drug for its receptor interferes with actions of endogenous agonists (1 mark)

6. a) What is the difference between mutagenesis and oncogenesis? (2 marks).

Answer: Mutagenesis is a process by which the genetic information of an organism is changed in a stable manner, resulting in a mutation. It may occur spontaneously in nature, or as a result of exposure to mutagens (1 mark). Carcinogenesis or oncogenesis or tumorigenesis is the 'creation' of cancer. It is the process by which normal cells are transformed into cancer cells (1 mark).

b) Name two human oncoviruses. (2 marks)

Answer: Any 4 from the following (1 mark each): HBV, HCV, HTLV, HPV, HHV8, EBV.
7. Below is the change in plasma concentration ($C_p$) of a new anticonvulsant immediately following a bolus dose.

![Graph showing plasma concentration over time](image)

a) By what route was this drug most likely administered? Explain your answer. (2 marks)

The oral route (1 mark). The maximum plasma concentration ($C_{\text{max}}$) is reached after a period of time taken for drug to transfer to central plasma compartment (1 mark).

b) What is the value of $C_{\text{max}}$? (1 mark)

$C_{\text{max}} = 5 \text{ µmol/L}$

c) What is the value of $T_{\text{max}}$? (1 mark)

$T_{\text{max}} = 15 \text{ h}$
d) Why might this administration route not be recommended in cases of clinical urgency? (2 marks)

This administration route takes several hours to reach $C_{\text{max}}$ and so considerable time may be needed to reach the steady state therapeutic level (1 mark). This is likely too slow to be effective in a clinically urgent situation, e.g. at onset of a seizure (1 mark).

8. The graph below shows the concentration-response curves for 4 drugs (named A-D) in a laboratory assay for smooth muscle function.

![Concentration-Response Curves](image.png)

a) Within the ‘drug effect spectrum’ describe the drugs A,B,C,D in terms of their behaviour at their receptor. (4 marks)

Answer: A= Full agonist, B=Competitive antagonist, C=Non-competitive antagonist, D=inverse agonist (4 marks)

b) What is the approximate $K_d$ of drug A? (1 mark)

Answer: Accept anything between $5 - 8 \times 10^{-6}$ Molar. MUST have units.
c) What does the behaviour of drug D tell you about the baseline activity of its receptor? (1 mark)

Answer: The receptor demonstrates ‘**constitutive activity**’ (1 mark).

d) Give the equation that relates maximal binding ($B_{\text{max}}$) to dissociation constant ($K_d$). (2 marks)

Answer: $B = B_{\text{max}} \times [C] / ([C] + K_d)$ (2 marks)

9. Consider the following case study: A 45 year old male suffers from occasional spastic paralysis of the lower limbs. He is prescribed an experimental anti-spastic drug which, in the laboratory, has been shown to act by reducing calcium ion binding to troponin. The drug significantly alleviates his muscle spasms but he reports multiple side effects including shortness of breath, oedema in his lower legs and inability to perform his usual exercise routines.

a) What is the likely cause of his side-effects? (1 mark)

Interference with normal cardiac function.

b) What are the similarities and differences in the mechanisms underlying contraction in different muscle types? (3 marks)

Any from (1 mark each): Both use Ca-troponin to structurally alter tropomyosin and expose actin binding sites. Both involve cross-bridge formation for force generation. Both use sodium channel activation to initiate excitation-contraction coupling. Skeletal muscle specialisations (T-tubules) ensure highly localised, transient calcium entry via VOCCs and consequent CACR via RyR. Cardiac muscle has global calcium entry – more calcium for longer, thus absolute effects of reduced calcium binding to troponin is less.

c) Why does he report no side effects related to gut function? (2 marks).

Smooth muscle in the alimentary system does not use troponin-calcium to expose myosin binding sites on actin (1 mark). Myosin light chain kinase (MLCK) phosphorylates myosin to facilitate contraction (1 mark)
SECTION C: Long answer question

Answer one question on the separate paper provided

Remember to write your candidate number at the top of the page and indicate whether you have answered question A or B

Mark total for this section: 30

EITHER

A) Why is liver and kidney function vitally important when considering drug dosing regimens? Discuss the role of these organs in drug metabolism and excretion (and the pharmacokinetic consequences), how they influence drug interactions and the role they play in drug toxicity.

Overview: Need to demonstrate understanding that these organs NEED to work together to determine the fate/function of a drug. 3 key steps: Phase 1 liver metabolism (hydroxylation, oxidation etc. – extra credit for demonstration of a chemical understanding of what these alterations in drug structure actually mean for reactivity, solubility, enzymes involved); Phase 2 liver metabolism (conjugation – vital for rendering drug molecules able to pass through kidney and into urine); Filtration in kidney – basic mechanism, importance of pKa, hydrophilicity.

Pharmacokinetic consequences: 1st pass description, timecourse of drug plasma concentration. Demonstrate understanding of how this pathway can be used to pharmacological benefit. Must demonstrate understanding of how timecourse of drug influences dosing frequency. Higher level of understanding demonstrated with compliance issues – solved with variable release formulations. Problems with absorption solved with prodrugs. Active molecule generated by phase 1 liver metabolism – consequences for pharmacokinetic profile. Biliary excretion and active reabsorption (enterohepatic pathway). Use of drugs that are excreted by the kidney in non-metabolised (i.e. active) state for bladder disorders. Understanding of how liver and/or kidney disease can alter PK profile.

Drug interactions: Pharmacokinetics of drugs may be influenced by other drugs that
share CYP systems. Demonstrate understanding of induction and inhibition of CYPs changing the metabolic fate of drugs. Examples are given in the lectures but there are MANY others. At least one example required.

Drug toxicity: Multiple pathways to toxicity owing to problems with liver/kidney function. Must demonstrate understanding of - the ‘therapeutic window’, that ALL drugs are toxic in sufficiently high plasma concentrations. Relate to ‘interactions’ component of the answer with specific reference to CYP inhibition. Example of underlying conditions that can elevate and prolong plasma concentration of a drug to toxic levels (egs given NFLD, alcoholism, polycystic kidney disease). Higher level understanding would include toxic metabolites of non-toxic drugs. Relation to pharmacogenetic factors: Generation by alternative metabolic pathways; deficits in metabolic enzyme function due to different isozymes present.

OR

B) Compound X is a potential novel nootropic (memory enhancing) drug acting to enhance calcium entry in neurons. Discuss, including mechanisms, the main consequences for synaptic transmission and suggest potential adverse effects of it’s administration.

Overview: Change in ionic calcium concentration in cytosol immensely potent pathway for drugs to influence cell function. Demonstrate understanding of the scope and nature of biological activity under the control of Ca relevant to the Q: Pre- and postsynaptic function, transcription and translation, cell structure, cell lifecycle and apoptosis. Demonstration of how calcium entry can be enhanced (VOCCs, LGCs, Kinase-linkedRs).

Main consequences:

1) Excitation-exocytosis. Underlying mechanism. Role of synaptotagmin. Source of calcium. VOCC subtypes involved. Role for release from SER for some transmitters/mediators (examples given – neuroinflammatory mediators, GPCR-coupled transmitters such as acetylcholine). Higher level answer would
demonstrate understanding of different pathways for mediator release and give examples relevant to neuronal function (examples given NO, AA, PG, CO).

2) Short-term plastic control of postsynaptic response to excitatory transmitter release. AMPA receptor phosphorylation changes unitary conductance of ionophore. Must demonstrate understanding of the dynamic nature of the phenomenon. The bi-directionality dependent on rate of activation of a given synapse. The pathways involved -PKA, CaMKII. Higher level answer would show how this phenomenon can be influenced by GPCRs and kinase-linked receptors (IP3, DAG, PKC).

3) Long-term control of postsynaptic response. Change in AMPA receptor number. Elevated Ca activated kinase cascades (eg given ERK in the Ras/Raf pathway) increases transcription/translation to boost AMPAR production. Interaction with TARPs to incorporate in postsynaptic membrane.

4) Stabilisation of dendritic spines: Spines localise Ca changes in cytosol. Ca entry via glutamate LGCs activates kinase pathways reorganising microtubule structure. Spine neck elongated and constricted.

Adverse effects:
How does drug X actually elevate Ca? If its synaptic use dependent then excessive synaptic plasticity can generate hypersynchronous states – epilepsy. If it is a general increase via neuromodulators then there is a danger baseline Ca could rise chronically. SER stores would cope with this until saturated. Then SER release via coupling to mitochondria would cause cristae remodelling, cytochrome c release and activation of caspase pathways leading to apoptosis. Resulting neurodegeneration irreversible and would detrimentally affect memory (correlates with AD, FTD given but many more).