B. 2 Opioid agonists and antagonists

a. Provide a brief overview of the history of morphine.

300 BC  juice extracted from papaverum somniferum described by Theophratus contains phenanthrines and isoquinolones (noscapine, papverine)
1400s  repopularized in Europe
1806  morphine isolated by Serturner
1853  syringe invented, morphine used with ether or chloroform GA
late C19  morphine-scopolamine anaesthesia tried, high mortality
1940s  semisynthetic opioids introduced: pethidine, methadone, nalorphine
1970s  opioid receptors differentiated

b. Explain the structure-activity relationships of the opioid agonists and antagonists.

All L isomers
Phenolic ring, quaternary carbon, 2 more carbons, amine group (highlighted)
4.55 Å from centre of phenol to N
Substitution of a larger group than OH at C3 reduces µ activity
Alkyl group at N produces an antagonist
Br or OH at C14 produces an antagonist

phenanthrines
extracted from papaverum somniferum
5 rings: morphine, thebaine, codeine
substitutions
  3,6 diacetyl ↑ lipid solubility: heroin
  3 methoxy ↓ µ agonism: codeine
  6 keto, NCH₂CH=CH₂, 14OH, 7-8 saturated:
      naloxone

morphinans
4 rings (no ether linkage): levorphanol,
dextromethorphan (has NMDA antagonist activity)

benzmorphans
3 rings (C6, 7 & 8 removed): pentazocine

phenylpiperidines
2 rings: pethidine, fentanyl, ~fentanils
5.66Å from ring to N
lipophilic chains on active N ↑ lipid solubility

peptides
endogenous opioid agonists
synthesized in endocrine and neural tissue
products all contain the same pentapeptide at the N terminal which is the opioid core
three precursors: pro-opiomelanocortin (produces hormones: ACTH, MSH, β-endorphin), pro-enkephalin and pro-dynorphin (produce neurotransmitters)
c. Explain the physiological nature and types of opioid receptors and the action of agonists, partial agonists, mixed agonist-antagonists and antagonists.

\( \mu_1 \)
- stimulated by opiates and opioid peptides
- \( \beta \)-endorphin > dynorphin > enkephalins
- endogenous ligand: met-enkephalin
- exogenous agonists: morphine, fentanyl
- G protein linked: ↑ K⁺ conductance, ↓ cAMP
  - protein kinase C activation ↑ wind-up
- supraspinal analgesia
  - ↓ prolactin, ACTH release, ↑ ADH, ACh turnover, catalepsy, feeding

\( \mu_2 \)
- stimulated by morphine
- G protein linked
- respiratory depression, ↓ gut motility, CVS depression (central)
- dopamine turnover, feeding, ↓ GH release

\( \delta \)
- stimulated by enkephalins
- \( \beta \)-endorphin = enkephalins > dynorphin
- G-protein linked: ↑ K⁺ conductance, ↓ cAMP
- spinal analgesia
- GH release

\( \kappa_{1,2,3} \)
- stimulated by opiates and dynorphin
- dynorphin >> \( \beta \)-endorphin >> enkephalins
- endogenous ligand: dynorphin
- exogenous agonists: ketocyclazocine, pentazocine
- ↓ Ca²⁺ channel conductance
- spinal analgesia
  - ↓ ADH, sedation, feeding

\( \varepsilon \)
- stimulated by \( \beta \)-endorphin
- endocrine role, ↓ immune function

\( \sigma \)
- no longer classified as an opioid receptor
- so-called agonists turned out to be NMDA agonists
- psychotomimetic effects
- morphine-3-glucuronide is an NMDA agonist
  - ↑ pain with high dose morphine, responsive to ketamine

mixed agonist-antagonists
- nalbuphene: \( \mu \) antagonist, \( \kappa \) agonist
  - may reverse respiratory depression without fully reversing analgesia
slow dissociating partial agonist
- buprenorphine: \( \mu \) partial agonist, high potency, slow dissociation
d. Explain the pharmacokinetics of the opioids and apply them to clinical usage, including infusion kinetics, transdermal, epidural, spinal and intramuscular usage.

<table>
<thead>
<tr>
<th>Protein Binding</th>
<th>$t^{1/2}_\alpha$ (min)</th>
<th>$t^{1/2}_\beta$ (h)</th>
<th>$V_d$ (l/kg)</th>
<th>clearance (ml/min/kg)</th>
<th>pKa</th>
<th>Lipid Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>35%</td>
<td>1.65</td>
<td>3.0</td>
<td>3.2</td>
<td>15.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Pethidine</td>
<td>65%</td>
<td>4-11</td>
<td>3-8</td>
<td>4.4</td>
<td>7.5-16.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>80%</td>
<td>13</td>
<td>3.6</td>
<td>4.0</td>
<td>13.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>90%</td>
<td>11.6</td>
<td>1.6</td>
<td>0.86</td>
<td>6.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>92%</td>
<td>17.7</td>
<td>2.7</td>
<td>1.7</td>
<td>13.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>70%</td>
<td>6</td>
<td>10min</td>
<td>0.35</td>
<td>40.0</td>
<td>1778</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>60%</td>
<td>3.3-5.7</td>
<td>4.3-5.6</td>
<td>10.9-17.8</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>90%</td>
<td>n/a</td>
<td>8-36</td>
<td>6</td>
<td>~0.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Codeine</td>
<td>n/a</td>
<td>3</td>
<td></td>
<td>3</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>1.5</td>
<td>1.0-2.5</td>
<td>3.6</td>
<td>27-35</td>
<td>7.9</td>
<td>high</td>
</tr>
</tbody>
</table>

Morphine is used intravenously, intramuscularly, subcutaneously, orally, intraarticular and occasionally nebulized. Its plasma levels do not correlate with clinical effect as its low lipid solubility causes slow equilibration across the blood-brain barrier. It has a high hepatic extraction ratio and so an oral bioavailability of only 30%. It is metabolized in the liver by glucuronide conjugation to morphine-3-glucuronide which is inactive and morphine-6-glucuronide which is active. These metabolites are renally cleared, so clinical effect of morphine is increased in renal failure though clearance remains constant. Metabolism is limited by hepatic blood flow.

Parenteral administration is commonly by intramuscular injection (0.1-0.2 mg/kg 3-4 hourly) or intravenous infusion for more constant plasma levels. Infusion is commonly at 1-5 mg/h in adults but a loading dose is required to achieve initial analgesia, typically 5-15 mg. Morphine is suitable for PCA. Epidural and spinal use are described but morphine is not the most suitable narcotic for this purpose as its low lipid solubility slows distribution, increasing the risk of central respiratory depression.

Pethidine is used intravenously, intramuscularly, epidurally and occasionally orally. It has an oral bioavailability of about 60%. It is metabolized in the liver to active and inactive metabolites, the most important of which is norpethidine which is a convulsant. Pethidine and its metabolites are renally cleared resulting in accumulation of metabolites in renal impairment. Its elimination half-life is prolonged in hepatic impairment.

Absorption from intramuscular injection is impaired in cold or vasoconstricted patients. When used epidurally, pethidine crosses the dura rapidly with CSF concentration peaking at about 15 minutes at the same time as plasma concentrations. It also crosses the placenta readily and has an elimination half-life in the newborn of 24 hours.

Dosing IV and IM is similar to morphine, with pethidine being about $1/10$ as potent. Epidural use is in the same dose range as IV use.

Fentanyl has a high lipid solubility and is used intravenously, epidurally and transdermally and can be used by other routes. In small doses its duration of action is determined by redistribution rather than elimination. Plasma concentrations correlate well with effect as it crosses the blood-brain barrier readily. It is metabolized in the liver by demethylation and hydroxylation to inactive metabolites which are renally cleared. A small amount may be secreted unchanged into the stomach and undergo recirculation.

Intravenous use is in two dose-ranges: 1-2 µg/kg as a coinduction or sedative agent and for brief duration analgesia and 30-100 µg/kg as an induction agent for cardiac anaesthesia alone or with N₂O. In the high dose range, its elimination half-life determines the duration of action. It can be combined with droperidol in neurolept anaesthesia.

Epidural use is common either alone or with a local anaesthetic agent. The dose range is 10-60 µg/h in adults. Fentanyl readily diffuses across the dura and also into blood.
Its high lipid solubility allows for transdermal use via patches (S-100) which deliver 50-100 µg/h. There is a long delay in reaching therapeutic plasma levels, so another analgesic is required to cover the first 6-8 hours. There is also a depot effect in the skin after a patch is removed. Use by intravenous infusion or intramuscular injection is uncommon as fentanyl is not well-suited to these uses because of its cost and short half-life.

Alfentanil is used intravenously. It is less lipid soluble than fentanyl but its low pKa results in most of the drug being in the unionized (basic) form at physiological pH, resulting in rapid diffusion across the blood-brain barrier. This, combined with a smaller V_d results in a more rapid onset of effect than fentanyl. Its elimination half-life is brief, so an infusion is required if it is to be used for anaesthesia.

It is metabolized in the liver to inactive metabolites by demethylation and dealkylation.

Sufentanil is pharmacokinetically similar to fentanyl.

Pentazocine is an opioid agonist(κ)-partial agonist(µ). It is used IM, IV and orally. It has a high extraction ratio and a bioavailability of 20%. Its hepatic metabolism is variable from patient to patient and is sensitive to hepatic impairment, with bioavailability rising to 70%. It is rarely used.

Codeine (3-methyl morphine) is used orally for analgesia and diarrhoea. It undergoes hepatic metabolism to inactive metabolites and also to morphine. Typical doses range from 8mg to 60mg q4h in adults.

Methadone is used orally for chronic pain and narcotic dependence and can be used IV. Its elimination half-life is markedly prolonged in chronic oral use. It has a low clearance by hepatic metabolism and so a low extraction ratio

Buprenorphine can be used IM, IV and sublingually.

Naloxone is an opioid receptor antagonist. It is used IM and IV for narcotic overdose. It is highly lipid soluble and has a short elimination half-life. It is metabolized in the liver by conjugation to glucuronide. Because its half-life is much shorter than most of the opioid agonists, repeat IM injection or IV infusion is required for treatment of overdose. Typical dose is 20-70 µg/kg IM or 5-10 µg/kg/h IV. Smaller doses are used to antagonize adverse effects of narcotic epidural infusions such as itch.

Naltrexone is an opioid antagonist with a lower extraction ratio than naloxone and so is used orally. It is used in an oral dose of 50 mg daily to help maintain alcohol and narcotic abstinence in dependent users who have withdrawn.

In principle, the loading dose and infusion rate of the narcotics used by IV infusion can be calculated from MEAC, V_d and clearance. In practice the dose is titrated against pain.

\[
\text{Loading dose} = \text{MEAC} \times V_d \\
\text{Infusion rate} = \text{MEAC} \times \text{clearance}
\]

e. Provide a detailed systematic description of the actions and pharmacodynamics of individual drugs: morphine, pethidine, pentazocine, diamorphine, methadone, fentanyl, alfentanil, sufentanil, codeine.

morphine
pharmacokinetics above
epidural, spinal use
slow distribution into spinal cord (10-15 min spinal, 15-60 min epidural)
prolonged duration due to low lipid solubility (12-20 h epidural)
late respiratory depression described
conjugated to morphine-6-glucuronide (potent analgesic)
and morphine-3-glucuronide (NMDA agonist)
also sulfated and N-demethylated
pharmacodynamics
potent µ and κ agonist
actions
supraspinal
cortex
anxiolysis, sedation, inhibition of REM sleep
EEG: ↑ voltage, ↓ frequency
mood effects: euphoria, dysphoria
stiffness
µ effect from inhibition of descending inhibitory motor pathway
from caudate nucleus
brainstem
respiratory depression
↓ CO₂, O₂ sensitivity (2˚ ↑ ICP if hypercapnia develops)
↓ cough reflex
CTZ: nausea, emesis
autonomic centres
↑ vagal tone (bradycardia)
↓ sympathetic tone
analgesia
opiate receptors in periaqueductal grey, NRPG
descending inhibitory pathways in DLF
spinal
inhibit slow EPSP resulting from C fibre stimulation
most potent as preemptive analgesia
itch: from either altered threshold or direct stimulation
peripheral
analgesic activity in periphery e.g. intraarticular use
cardiovascular
direct effect on SA node to ↓ rate
haematological
direct effect on mast cells to degranulate and release histamine
gastrointestinal
smooth muscle spasm, damages anastomoses
↓ LOS tone, ↓ motility
genitourinary
↓ urine output (via ADH)
↑ detrusor and sphincter tone
endocrine (? via D₂ agonism)
↓ ACTH, prolactin, GHRH
↑ ADH
clinical use
MEAC ≈16 ng/ml
administered by all routes except rectal, transdermal and topical
pethidine
synthetic opioid developed as an anticholinergic (1939)
pharmacokinetics above
N-demethylated to norpethidine
50% analgesic potency, cerebral irritant
renally cleared
then hydrolyzed to normeperidinic acid
t_{1/2} 24 h in the neonate, fetal:maternal concentration ratio ≤1.0
epidural use
plasma levels peak after 10-15 min, rapid CSF penetration 15-30 min
pharmacodynamics
10% potency of morphine
µ and κ agonist
local anaesthetic, type I antidysrhythmic
anticholinergic
actions
as for morphine except:
cerebral
irritation and convulsions with accumulation of norpethidine
less miosis due to anticholinergic effect
respiratory
same reduction in ventilation, but ↓ TV with little fall in rate
cardiovascular
not suitable for cardiac use because of membrane stabilizing effect
mild vasodilator
gastrointestinal
less spasm and constipation than morphine, but still ↓ motility
clinical use
MEAC ≈ 0.5 µg/ml
fentanyl
synthetic phenylpiperidine-related opioid
alfentanil and sufentanil differ only in potency and pharmacokinetics
pharmacokinetics
rapid redistribution and slow elimination
high hepatic extraction ratio
metabolized by N-dealkylation and hydroxylation
pharmacodynamics
potent µ and κ agonist
100 times potency of morphine
actions
similar to morphine except:
cardiovascular
little effect alone, no histamine release
hypotension in large doses in conjunction with diazepam
endocrine
suppresses stress response
clinical use
MEAC 3 ng/ml
anaesthesia > 20 ng/ml
two dose ranges
coinduction 1-2 µg/kg
cardiac 30-100 µg/kg
pharmacokinetics unpredictable at intermediate doses
transdermal use occasionally
skin produces a 12-hour depot “compartment”

pentazocine
a benzomorphan
only the L-isomer is active, but it is supplied as a racemic mixture
pharmacokinetics
20% bioavailable
high extraction ratio
oxidized and glucuronidated
metabolism greatly impaired in alcoholism
pharmacodynamics
  \( \mu \) partial agonist, \( \kappa \) agonist, NMDA agonist
  approximately 30% as effective as morphine as an analgesic
actions
  similar to morphine except
  respiratory
    ceiling to \( \mu \) effects: respiratory depression and supraspinal analgesia
  cardiovascular
    ↑ sympathetic outflow, mild ↑ MAP and HR