**1997a(9): Briefly describe the pharmacological role of the nicotinic acetylcholine receptor**

General: nicotinic AChR (nAChR) is a **ligand gated** receptor with a **central cation ionophore**

*Structure:* Pentameric
- 2α, β, γ, δ (ε in fetal NMJ)

*Location:*
- Postysynaptic on the **motor endplate** (NMJ)
  - Motor endplate depolarisation → contraction of skeletal muscle
- Presynaptic (nerve terminal)
  - Positive feedback mechanism to ↑**mobilisation / release** of ACh
- Autonomic ganglia (sympathetic / parasympathetic)
  - Depolarisation postganglionic neurons → ↑firing
- Adrenal medulla
  - Catecholamine release
- CNS
  - Various undefined responses

*Ligand*: ACh must bind to both **α subunits**
- Synthesised in nerve axoplasm
- Stored in **vesicles** of presynaptic nerve terminal

*ACh Release*:
- Motor nerve action potential → exocytosis of vesicles and release of ACh into cleft → ~200 vesicles released (Ca dependent mechanism)

*nAChR Activation*:
- ACh diffuses across cleft → binds nAChR
  - 2 molecules ACh required to activate receptor
- Activation: Conformational change → opening of **central ionophore**
  - Influx cations (1° Na, also K, Ca)
- Causes local reversal of membrane potential (EPP)
  - Summate many EPP → reach threshold (-10mV) → opening of voltage gated fast Na channel → membrane depolarisation → AP
- **Antagonists** of NMJ (NMBD)
  - Compete with ACh for binding sites
  - Depolarising NMBD (sux) will activate nAChR but maintain it in open state → unable to generate more AP
  - Non-depolarising NMBD (vec, roc, atra, cisatra) → competitive blockade of nAChR, nil intrinsic agonist activity
    - Blockade

*nAChR Inactivation*:
- Rapid hydrolysis by **acetylcholinesterase** in synaptic cleft
  - Each molecule stimulates only 1 receptor for 1ms
- **Inhibitors of AChE**
  - Prevent hydrolysis of ACh in NMJ → ↑availability of ACh for activation of multiple nAChR
  - Useful in reversal of NMBD → ↑substrate available for competition → reverses competitive blockade

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**1997b(16): Describe the location and function of dopamine receptors. Give examples of agonists and antagonists**

General: Dopamine is an endogenous sympathomimetic

- Dopamine receptors are present throughout the **CNS** and **PNS**
- Receptors are classified 1-5

**$D_1$R** ($D_5$)

- Postsynaptic
- Location: vessel smooth muscle
  - Renal, mesenteric, coronary, cerebral
- Receptor type: GPCR ($G_s$)
  - ↑adenylyl cyclase → ↑cAMP
- Stimulation: produces **vasodilation**

**$D_2$R** ($D_3$, $D_5$)

- Presynaptic
- Location:
  - CNS
  - PNS: Noradrenergic nerve terminals of vascular smooth muscle
    - Vasodilation via ↓NA release
- Receptor type: GPCR ($G_i$)
  - ↓adenylyl cylase → ↓cAMP
- Stimulation: ↓NA release from nerve terminal
  - Role in reward pathway
  - N&V

**CNS Function**

- Limbic system: mood, emotional stability
  - ↑activity DR → perceptual disturbance (psychosis)
- CTZ: N&V
- Basal ganglia (corpus striatum / substantia nigra): movement modulation
  - Balances ACh stimulation
- Pituitary
  - Tonic inhibition of PRL release

**Agonists**

- L-Dopa (prodrug): carboxylated dopamine → good PO availability → dexcarboxylated → ↑lipid solubility → cross BBB → central effect
- Apomorphine
- Bromocriptine

**Antagonists**

- Phenothiazines
  - Prochloperazine, chlorpromazine, promethazine
- Butyrophenones
  - Droperidol
  - Haloperidol
- Clozapine
- Benzamide
  - Metaclopramide

By Amanda Diaz

**2002a(16): Briefly outline the pharmacology of flumazenil**

General: Major inhibitory neurotransmitter in the CNS is GABA

- Binds to $GABA_AR$ (ionotropic) and $GABA_BR$ (metabotropic)

**$GABA_AR$**: pentameric receptor with central ion pore. Comprised 2α, 2β, γ subunits

- GABA binding site on β subunits → binding causes opening of central $Cl^-$ channel and subsequent cell membrane hyperpolarisation
- Contains specific binding sites for **barbiturates**, **alcohol, benzodiazepines**

**Benzodiazepines**

- Bind to BZ receptor (α subunit) → ↑affinity for GABA → ↑frequency of $Cl^-$ channel opening

**Flumazenil**: 1,4-imidazobenzodiazepine

*Physicochemical*

- Chemical: Imidazobenzodiazepine
- Presentation: Clear / colourless solution 100µg/ml (5mL)
- Route of administration: IV only

*Pharmacodynamics*

- Specific benzodiazepine receptor **competitive antagonist**
  - High receptor affinity
  - Minimal agonist activity
- MOA: **dose-dependent** prevention / reversal of effect of benzodiazepines
- Uses: 'wake up' test in scoliosis surgery; treatment BZ OD
- Dose: Initial 0.2mg IV → reversal expected in 2min
  - 0.1mg IV at 60s intervals titrated to effect (max 1mg)
  - Continuous low-dose infusion 0.1 – 0.4mg/hr
- Duration of action: 30 – 60 min
  - May require repeat dosing (duration effect < benzo's)
- S/E: Minimal likely 2° weak intrinsic agonist activity

*Pharmacokinetics*

Absorption: Good PO absorption → extensive 1$^{st}$ pass metabolism

Distribution: 50% protein bound (1° albumin)

- Vd 1L/kg

Metabolism: Carboxylic acid & glucoronide (inactive)

Elimination: Urine; <0.1% unchanged

- CL = 10 – 14ml/kg/min
- $t_{½\beta}$ = 53min

**2003b(3)/2001a(10): Outline GABA's role as a neurotransmitter and indicate how its actions may be modified by pharmacological agents**

General: γ-aminobutyric acid is a neurotransmitter

- derived from glutamate
- 1° inhibitory neurotransmitter in brain
- Binds GABA receptors
    - $GABA_AR$
    - $GABA_BR$

**$GABA_AR$**

- α, β, γ δ subunits available → homomeric / heteromeric possible
- 1° postsynaptic
- Ionotropic receptor → pentameric receptor with central $Cl^-$ channel → opening → cell hyperpolarisation
- β subunit: GABA binding site
    - Antagonist at GABA binding site: bicucculine
- α subunits
    - Benzodiazepine receptors (BZ1 / BZ2): potentiate effects of $GABA_AR$ by ↑affinity for GABA → ↑$Cl^-$ conductance
        - Requires GABA
- Other drug effects:
    - Barbiturates → potentiate $Cl^-$ conductance
        - Low dose: Requires GABA
        - High dose: Activation in absence of GABA
    - Propofol → direct stimulation of $GABA_AR$
    - Progesterone → potentiates $Cl^-$ conductance
    - Alcohol / VA / GHB → potentiate $Cl^-$ conductance
        - Mechanisms unknown
    - Flumazenil → competitive antagonist (dose-dependent reversal) → min intrinsic activity → ↓BZ-related $Cl^-$ conductance potentiation

**$GABA_BR$**

- Presynaptic
- Metabotropic receptor → GPCR → leads to ↑$K^+$ conductance → cell hyperpolarisation
- Drug Effects:
    - Baclofen → agonist, potentiates GABA effect
    - Phaclofen → (non-therapeutic) antagonist

**2004b(3)/1998a(9): List the effects of histamine. Write a brief outline on the pharmacology of the $H_1$ receptor blocking drugs**

General: Histamine is an **endogenous amine** stored in **granulated vesicles** of mast cells and basophils

- Found in most tissues of body
  - Highest concentrations lung, skin, GIT
- Non-mast cell mediated histamine → located in brain where is acts as a **neurotransmitter**

**Histamine Receptors** → named according to response to specific blocking drugs

**H1**

- GPCR → phospholipase C → IP3, DAG → ↑$Ca^{2+}$
- Respiratory tract: Bronchial smooth muscle (↑tone); ↑mucous secretion
- Vessels:
  - Vasodilatation 2° ↑NO production **flare, erythema**
    - ↓intravascular vol (shock)
  - ↑vascular permeability → swelling, angioedema **wheal**
  - ↑prostacyclin production → vasodilatation, ↓platelet aggregation, ↑**airways resistance**
- Heart: ↓conduction AV node; coronary artery vasoconstriction
- CNS: post-synaptic excitatory
- Skin: Stimulation of cutaneous nerve endings **pruritis**

**H2**

- GPCR → ↑adenylyl cyclase → ↑cAMP
- GIT: ↑gastric acid production (parietal cells)
- Heart: coronary artery vasodilation; positive inotrope / chronotrope
- CNS: post-synaptic inhibitory

**H3**

- Used only in research
- CNS: pre-synaptic inhibitory (?negative feedback role)

**H1R** antagonists → Reversible competitive antagonists

**1st Generation** → Cross BBB (central acting)

- Promethazine (Phenergen)

*Pharmacodynamics*

- MOA: H1R blockade, also anticholinergic effects (small anti-5HT, antiD)
- Use: antihistamine, antiemetic, sedative
- CNS:
  - potent sedative
  - central antiemetic (block vestibular stimulation of CTZ)
  - anxiolytic
  - slightly antanalgesic
- CVS:
  - Nil effect at therapeutic dose
  - Transient ↓MAP with rapid IVI
- Resp:
  - Bronchodilation

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    - ↓secretions
    - Antiptussive
- GIT: ↓LOS tone
- Toxicity:
    - Anticholinergic → extra pyramidal reactions (dystonia) in high doses; excitatory phenomena
        - Dry mouth, blurred vision, urinary retention
    - Sedation
    - Overdose: Seizures, coma, death

*Pharmacokinetics*

Absorption: extensive 1st pass metabolism

Distribution: Vd 2.5L/kg

- Highly protein bound (93%)

Metabolism: Hepatic (sulphoxidation, N-dealkylation)

Elimination: Urine; 2% unchanged

- CL 1.4L/min
- $t_{½\beta}$ 8hrs

**2nd Generation** → not central acting (do not cross BBB)

- Fexofenadine (Telfast)

*Pharmacodynamics*

MOA: Reversible competitive inhibition

CVS: As above

CNS: Nil cross BBB; nil anti-emetic; nil sedative effect

Resp: as above

*Pharmacokinetics*

As above

**2007a(7): Describe the pharmacology of midazolam including its mechanism of action**

Short acting BZ.

**Physicochemical:**

- Clear colourless sol$^{n}$ – 1,2,5mg/ml
- pH soln – 3.5
    - pH < 4: Open ring structure → $H_2O$ soluble
    - pH > 4: Closed ring → ↑lipid solubility
- pKa: 6.5, basic drug
    - pH 7.4 89% unionised

**Pharmacodynamics**

- Use: sedative, hypnotic, anxiolytic, anticonvulsant
- MOA: Binds to BZ receptor of $GABA_AR$ α subunit
    - Potentiates effect of GABA → ↑freq opening of intrinsic $Cl^-$ channel
- CNS: dose-dependent ↓$CMRO_2$ / ↓CBF; antinociceptive in SC/epidural
- CVS: May ↓BP on rapid injection
- Resp: °effect MV. ↓TV / ↑RR. Chemoreceptors intact.
- Interaction:
    - metabolised by same CYTP450 system as alfentanil → co-administration prolongs effect
    - MAC sparing
    - Blunts response to instrumentation of airways with fentanyl

**Pharmacokinetics**

*Absorption*: Oral bioavailability 40%; IM/intranasal; IV

*Distribution*: Vd 1-1.5L/kg; 95% PB (albumin)

*Metabolism*: Short duration of action 2° rapid distribution

- Liver metabolism (almost complete) → hydroxylation (to active compound) → then glucoronid$^{n}$

*Elimination*: Urine

- $t_{½\beta}$: 1-4hrs
- CL: ~7ml/kg/min (> diazepam)

**MAKEUP: Compare and contrast the pharmacology of diazepam and midazolam**

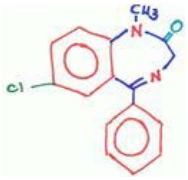
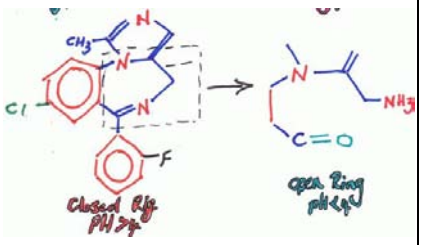
General: Both are benzodiazepines

- Act by potentiating the effect of GABA on the $GABA_AR$ in the CNS
  - Binds to specific BZ binding site (α subunit)
  - ↑affinity of receptor for GABA → ↑opening frequency of channel
- Activation of receptor → opening of central ionophore → ↑influx $Cl^-$
  - Cell hyperpolarisation
  - ↓depolarisation

**BZ receptor**

2 subtypes found

- BZ1 → located in **spinal cord** and **cerebellum**
  - Effect: Anxiolysis
- BZ2 → located in **spinal cord**, **hippocampus**, **cerebral cortex**
  - Effect: Sedative; anti-convulsant

| | **Diazepam** | **Midazolam** |
|---|---|---|
| *Physicochemical* | | |
| Structure |  |  |
| Chemical | Benzodiazepine | Imidazobenzodiazepine |
| Presentation | Tablets 2, 5, 10mg<br>Suppository 10mg; 2, 4mg/ml $sol^n$<br>$Sol^n$ dissolved in benzyl alcohol (clear, painful); oil:$H_2O$ (less pain)<br>5mg/ml | Clear colourless solution 1, 2, 5mg/ml |
| pKa | | 6.15<br>Solution buffered to 3.5 2° **pH-dependent ring-opening phenomena:**<br>**Open pH < 4 = $H_2O$ sol**<br>**Closed pH > 4 = lipid sol** |
| Route of Admin | PO: 2-60mg/day<br>IVI: 10-20mg | IM / IV: 0.02-0.2mg/kg<br>Infusion: 0.02-0.2mg/kg/hr<br>Effect in ~10min; last 20-60min<br>Intranasal / PO: 2-3 x IV<br>Intrathecal: 0.3-2mg<br>Epidural: 0.1-0.2mg |
| *Pharmacodynamics* | | |
| MOA | BZ → potentiates GABA effect $GABA_AR$<br>κ-opioid agonist *in vitro* ?role in spinal analgesia | BZ → potentiates GABA effect on $GABA_AR$<br>κ-opioid agonist *in vitro* ?role in spinal analgesia |
| Use | Anxiolytic; hypnotic; sedative<br>Antiepileptic<br>Relieve muscle spasm | Induction<br>Sedation<br>Anxiolytic |

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| | Alcohol withdrawal | Anticonvulsant |
|---|---|---|
| CVS | Transient ↓MAP / ↓CO with rapid IVI<br>Coronary vasodilation<br>↓cardiac mm $O_2$ requirements | ↓MAP (5%); ↓SVR<br>Reflex ↑HR<br>Obtund pressor response to intubation |
| Resp | Large dose → resp depression<br>Depressed hypoxic response (> than depressed hypercarbic) | ↓TV / ↑RR (compensated)<br>MV unchanged<br>Apnoea → variable b/n Pts<br>↓vent response ↑$pCO_2$ |
| CNS | Sedation; hypnosis<br>↓aggression<br>Paradoxical excitation esp in elderly<br>Anterograde amnesia<br>Anticonvulsant<br>Analgesic<br>Depresses spinal reflexes | Rapid cross BBB but **slow effect-site equilibrium (0.9-5.6 min)**<br>Hypnosis; sedation<br>↓aggression<br>Anterograde amnesia<br>Neuraxial use → antinociceptive<br>↓$CMRO_2$ / CBF |
| Other | Nil | ↓adrenergic response to stress<br>Nil effect cortisol / RAA<br>Cross placenta / breast milk<br>↓PONV |
| Toxicity / SE | Drowsiness; ataxia; headache<br>Rash<br>GI upset<br>Urinary retention<br>Tolerance / dependence occur<br>Withdrawal syndrome may occur<br>IVI irritant (benzyl alcohol prep) | Withdrawal syndrome in children with prolonged use |
| Interactions | ↓MAC<br>↓by drugs competing for cytP450 system (cimetidine) | ↓MAC<br>Prolonged action if used $^{w}$/alfentanil → same cytP450. |
| *Pharmacokinetics* | | |
| Absorption | Rapid PO → bioavailability 85-100%<br>Slow erratic IMI absorption | PO: bioavailability 44% 2° extensive 1$^{st}$ pass |
| Distribution | 1-1.5L/kg<br>95% protein bound (alb/AAG) | 1-1.5L/kg<br>95% protein bound<br>Highly lipophilic with closed ring → short duration action 2° dist$^{n}$ |
| Metabolism | Hepatic → active metabolites<br>N-demethylation (oxidising) → **desmethyldiazepam** v active ($t_{½}$ > 100hrs) → must be gluc$^{n}$ for excretion**<br>**Oxazepam** →gluc$^{n}$ (inactive), **temazepam**→gluc$^{n}$ (inactive) | Hepatic → Hydroxylation<br>Glucoronidation<br>Compounds not clinically active<br>CL **x10 cf diazepam** |
| Elimination | Urinary; <1% unchanged<br>CL: 0.2-0.5ml/kg/min *↓with concurrent use halothane*<br>$t_{½β}$: 20-40hrs | Urine; <1% unchanged<br>CL: 6-10ml/kg/min<br><br>$t_{½β}$: 1-4hr → may be **x2 in elderly** |

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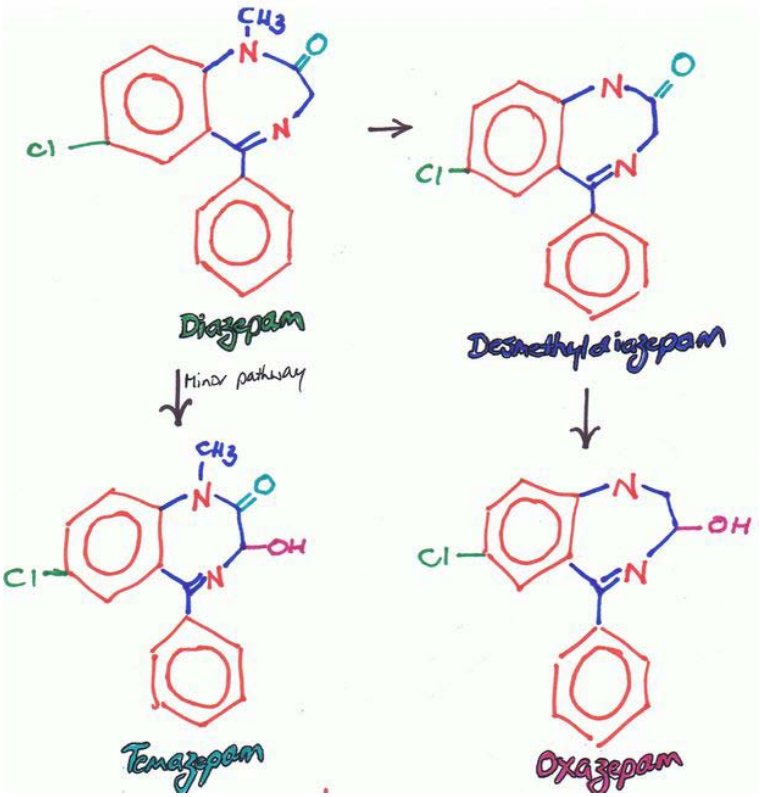


By Amanda Diaz

MAKEUP: Write short notes on the pharmacology of 5-HT

General: 5-hydroxytryptamine (serotonin)

- widely distributed
- Endogenous **vasoactive** substance
  - Vasoconstriction: cerebral, coronary, pulmonary vasculature
- **Neurotransmitter**
  - Emesis
  - Pain
- Location: 90% in GIT, 10% within platelets / CNS
  - Unknown function in platelets → ?mop-up from released serotonin

**5-HT Receptors**

Classified 1 – 4

- 5-$HT_1$: $G_i$ → ↓adenylyl cyclase → ↓cAMP
  - 1a, 1b: CNS → behavioural effects (sleep, thermoregulation)
  - 1d: CNS → vasoconstriction
    - *agonist: sumitriptan*
- 5-$HT_2$: $G_p$ → ↑phospholipase C → ↑$IP_3$, DAG → ↑$Ca^{2+}$
  - 2a: CNS/PNS; smooth muscle; platelets
    - *agonist: LSD;*
    - *antagonist: ketaserin*
  - 2b: Gastric fundus → ↑contraction
  - 2c: CNS → ↑CSF production
- 5-$HT_3$: Direct activation $Na^+$ and $K^+$ channels (non-GPCR)
  - PNS/CNS → visceral pain, N&V (CTZ), anxiety
    - *antagonists: ondansetron, tropisetron*
- 5-$HT_4$: $G_s$ → ↑adenylyl cyclase → ↑cAMP
  - Brain
- 5-$HT_{5-7}$: $G_s$ → ↑adenylyl cyclase → ↑cAMP
  - Brain

**Serotonin Antagonists**

- SSRIs (fluoxetine) → act on most receptor subtypes
  - Can trigger **serotonin syndrome**: confusion, agitation, HT, ↑HR, arrhythmias, ↑temp, DIC
  - Treatment: benzodiazepine (lorazepam)
- 5-$HT_3$ (ondansetron) → PO bioavailability 60%
  - Metabolism: hepatic → inactive glucoronides / sulfates
    - ↑duration of action inb hepatic failure
  - S/E: headache, light-headedness, constipation / abdominal pain

By Amanda Diaz