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Anxiolytics and Hypnotics:
Pharmacodynamics in Action

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Aims and Objectives

Knowledge of basic psychopharmacology

- Neurotransmission
- Receptor Types
- Examples of neurotransmitters
- Pharmacodynamic principles
- Tolerance and sensitisation

With reference to anxiolytics and hypnotics

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What is Anxiety?

It can be a normal response to a threatening situation

It can also appear without obvious triggers

It is adaptive response; it signals potential danger

Excessive anxiety is maladaptive
(too intense/ inappropriately provoked)

- Panic disorder
- Phobic anxiety
- GAD
- PTSD
- OCD

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Definitions

Anxiolytic:

A medication used to reduce anxiety symptoms.

Sedative:

Slows down functional activity, calming.
Relaxing, calming, soothing effects.
Having a soothing, calming, or tranquilizing effect; reducing or relieving anxiety, stress, irritability, or excitement.

Hypnotic:

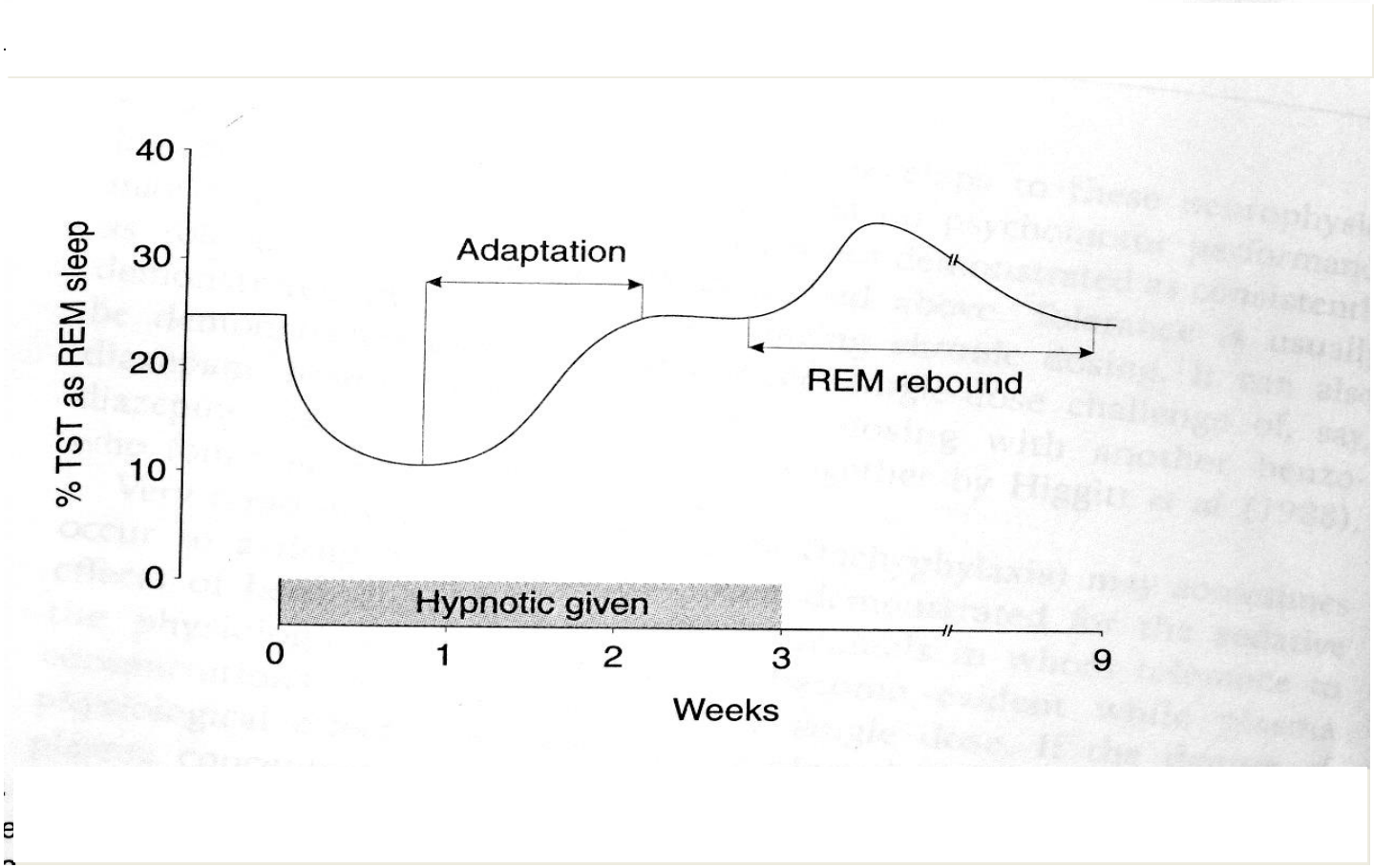
Tends to produce sleep.
Anything that induces hypnosis, trance state or sleep.
A medication that causes drowsiness, induces sleep onset, and/or maintains sleep.

Sleep

Stage (% TST)	EEG	Sleep state	Physiological state
I (2-5%)	Low amplitude, mixed frequency	Drowsy or shallow sleep	Slow, rolling eye movements
II (67-75%)	As I + sleep spindles & K-complexes	Asleep (light)	No eye movements ↓ HR, RR, Mus tone
III	Mod high amplitude, slow freq (<2Hz)	Asleep (slow wave sleep) (deep)	As Stage II
IV (+III – 15-25%)	Large amount high amplitude, low freq activity	Asleep (slow wave sleep) (v deep)	As Stage II
REM (25-33%)	Low-amplitude, mixed-frequency (like stage I)	Dreaming	Bursts of REM, loss of Mus Tone, ↑ HR, BP, RR, Cere BF

Effects of Hypnotics on Sleep

Increased REM rebound: increased dreaming, nightmares, nocturnal awakening



Neurotransmission

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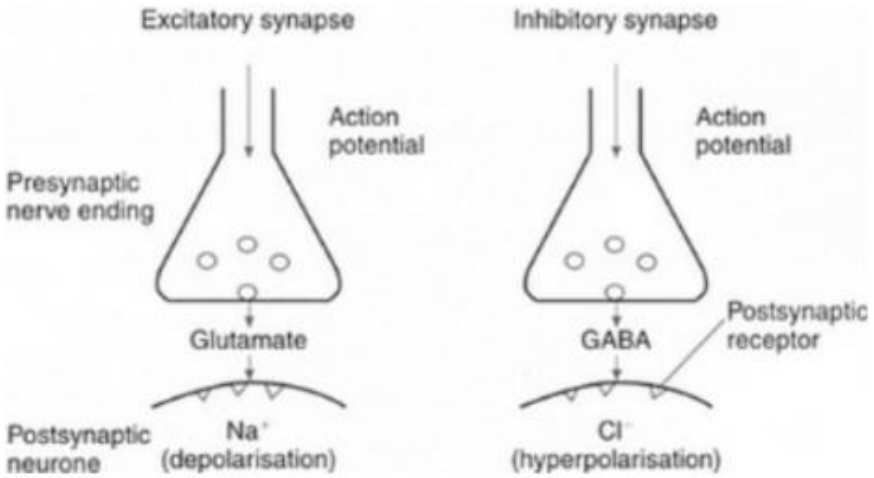
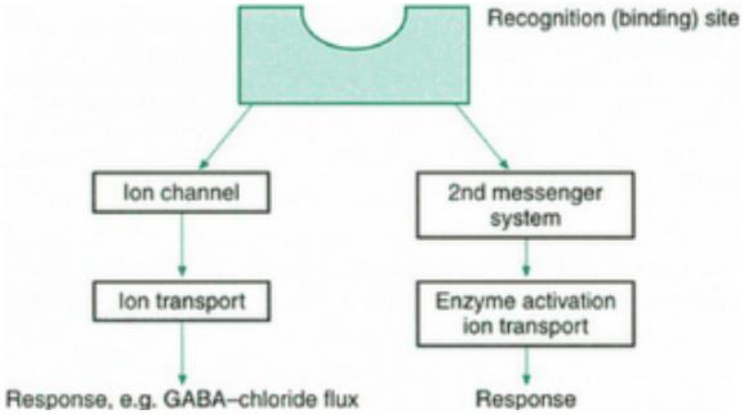
Neurotransmission – process by which information is transferred from one neurone to another across the synapse



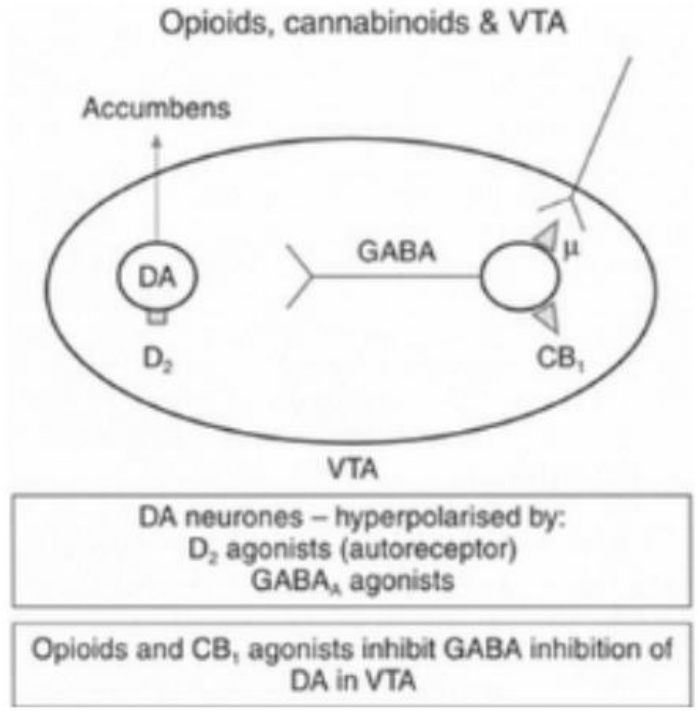


Activation of the postsynaptic receptor may result in:

- **Excitation** – membrane depolarisation
- **Inhibition** – membrane hyperpolarisation

Neurotransmission

- The initial receptor response (excitation/inhib) does not necessarily describe the final functional output



Opioids

Cannabinoids

Co-existence of Neurotransmitters

- Some substances released from nerve endings act as neuromodulators
- DA, NA, 5-HT and Ach – commonly co-exist with various neuropeptides, e.g. cholecystokinin (CCK), neurotensin (NT) and thyrotrophin releasing hormone (TRH); which act as either:
  - Full NTs (i.e. produce a functional response of their own);
  - As neuromodulators (when they modulate the responsiveness of the amine neurotransmiter)

Organisation of Neurotransmitter Pathways

The major NT pathways can be organised into 3 groups:

- **Long ascending and descending axonal pathways derived from discrete neuronal cell groups located within specific brain nuclei**
  - This is seen with catecholamine (DA/NA) and indolamine (5-HT), as well as many cholinergic (ACh) pathways.

- **Long and short axonal pathways derived from neuronal cell bodies widely distributed throughout the brain**
  - associated with the major excitatory (glutamate) and inhibitory (GABA) NTs. They lack the very precise organisation structures of the amine pathways.

- **Short intraregional pathways**
  - Often associated with GABA inhibition, but also various neuropeptites (e.g. somatostatin in the cerebral cortex).

Receptor Mechanisms

Receptors for NTs can be:

- Directly coupled to an ion channel (ionotropic), so concerned with fast neurotransmission, e.g. NMDA, $GABA_A$ and nicotinic types of Ach receptors
- Coupled to an intracellular effector system via G-protein (metabotropic receptors) and so concerned with slow neurotransmission (e.g. DA, NA, most 5-HT and muscarinic Ach receptors)
- Linked to other systems, such as the membrane kinase linked receptors (growth factors, insulin) and intracellular receptors that control gene transcription (steroids)

Ion Channel Linked Receptors

Ion channel-linked receptors are protein structures containing about 20 transmembrane segments arranged to form a central channel

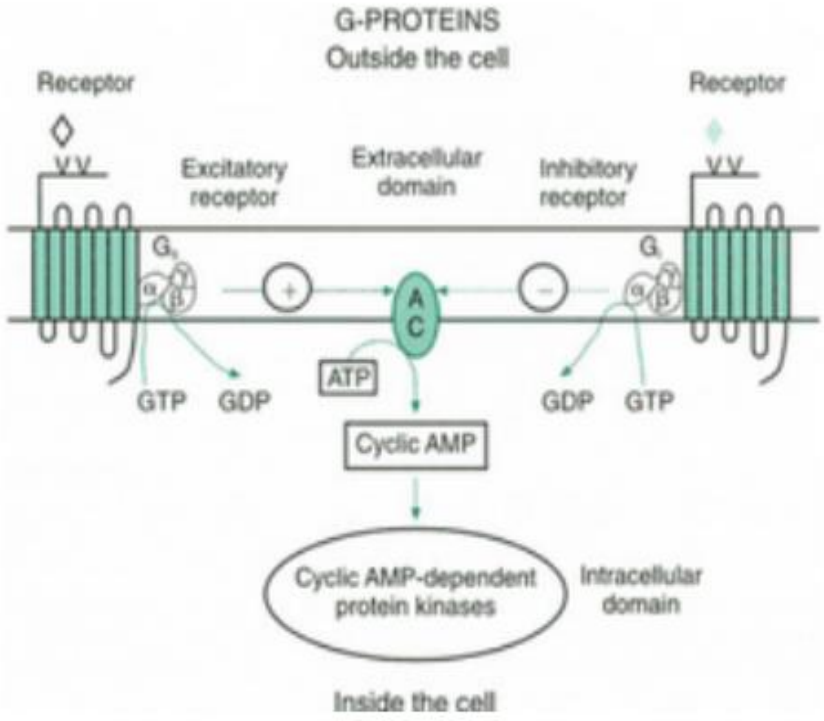
Binding of the transmitter to the receptor opens the channel to specific ions

Ion channel opening occurs in milliseconds

G Protein Receptors

G protein has 3 subunits (α,β,γ) with the α unit containing GTPase activity
When the transmitter or agonist binds to receptor, it can either activate or inhibt one of 2 major second messenger systems

- cAMP – activates various protein kinases
- Phospholipase C/ IP_3/ DAG



G Protein Receptors

The amine NT's (DA, NA, 5-HT and Ach), generally act as slow excitatory or inhibitory transmitters depending upon their receptor coupling system

(Some amine receptors are directly coupled to ion channels (5-HT_3, nicotinic, Ach receptors))

Glutamate

Glutamate is an example of a fast acting excitatory NT, where the receptors (NMDA, AMPA) are directly liked to a Na^+ channel

Gamma-aminobutyric Acid -GABA

GABA is the major fast acting inhibitory neurotransmitter

GABA, converted from the principal excitatory neurotransmitter glutamate in the brain, plays a role in regulating neuronal excitability by binding to its receptors, GABA-A and GABA-B, and thereby causing ion channel opening, hyperpolarization and eventually inhibition of neurotransmission

Traditional hypnotics and anxiolytics modulate GABA transmission

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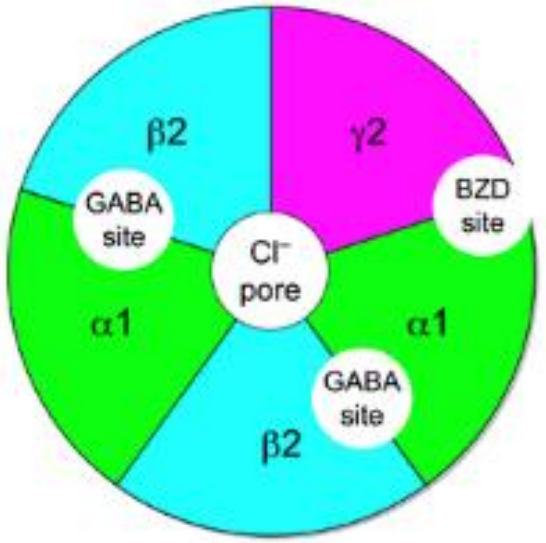
$GABA_A$ – BDZ Receptor Complex

Five subunits arranged in rosette
Meeting in centre forming a channel for Cl^- ions

Separate binding site for GABA and BDZ

Two molecules of GABA to open the ion channel

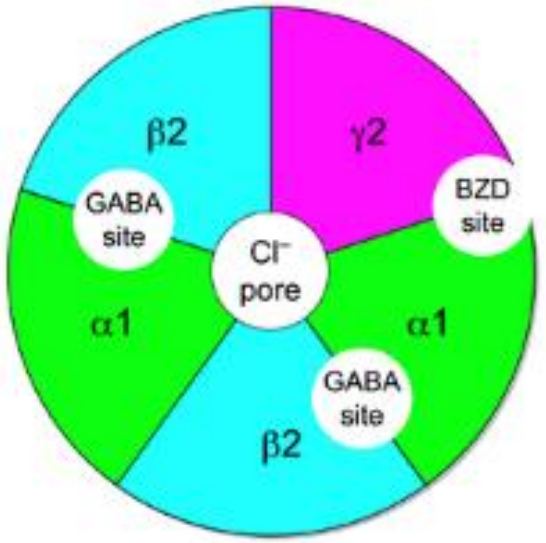


$GABA_B$ receptor are G-protein coupled receptors and are not allosterically modulated by BDZ. It does not appear to have anxiolytic properties

$GABA_A$ – BDZ Receptor Complex

The $GABA_A$ receptor is composed of five subunits, the most common ones being two *α*s, two *β*s, and one *γ* ($\alpha_2\beta_2\gamma$).

For each subunit, many subtypes exist ($\alpha_{1–6}$, $\beta_{1–3}$, and $\gamma_{1–3}$).



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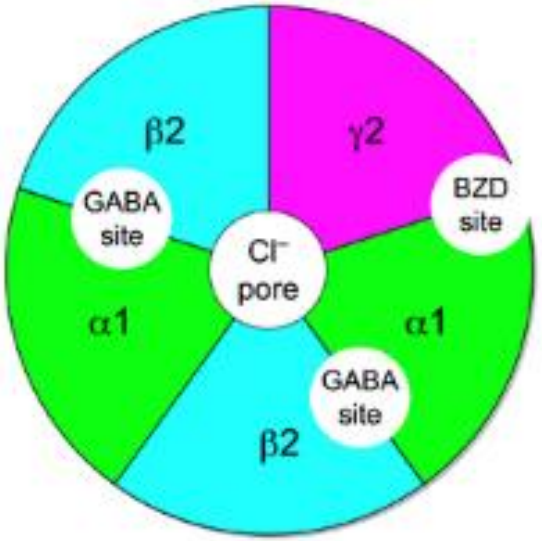
$GABA_A$ – BDZ Receptor Complex

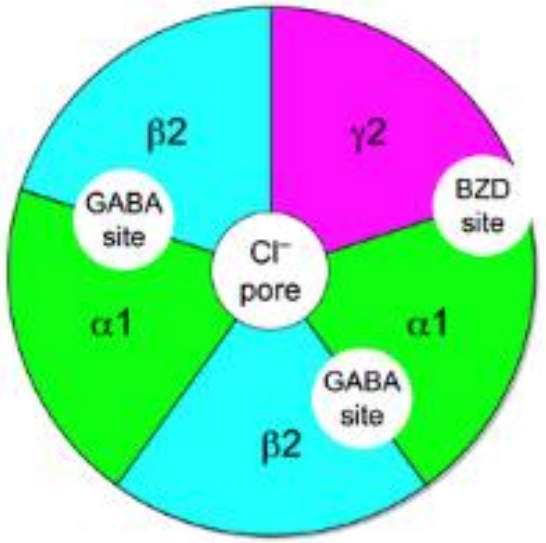
$GABA_A$ receptors that are made up of different combinations of subunit subtypes have different properties, different distributions in the brain and different activities relative to pharmacological and clinical effects



$GABA_c$ - $GABA_A$-ρ receptor : is a subclass - composed entirely of rho (ρ) subunits. is expressed in many areas of the brain, but in contrast to other $GABA_A$ receptors, the $GABA_A$-ρ receptor has especially high expression in the retina.

$GABA_A$ – BDZ Receptor Complex

Opening of the channel allows Cl^- to flow into the cells
Leading to hyperpolarization and inhibition of the activity.



Wide spread and mediate inhibition in cerebral cortex, amygdala and brain stem (modulating 5HT and nor-adrenergic cell bodies)

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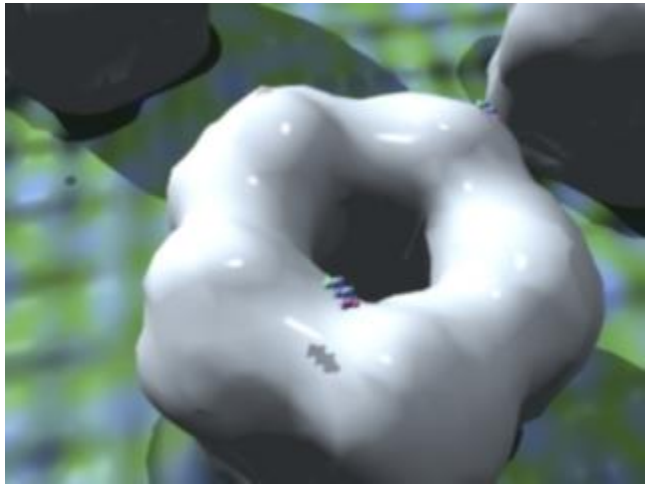
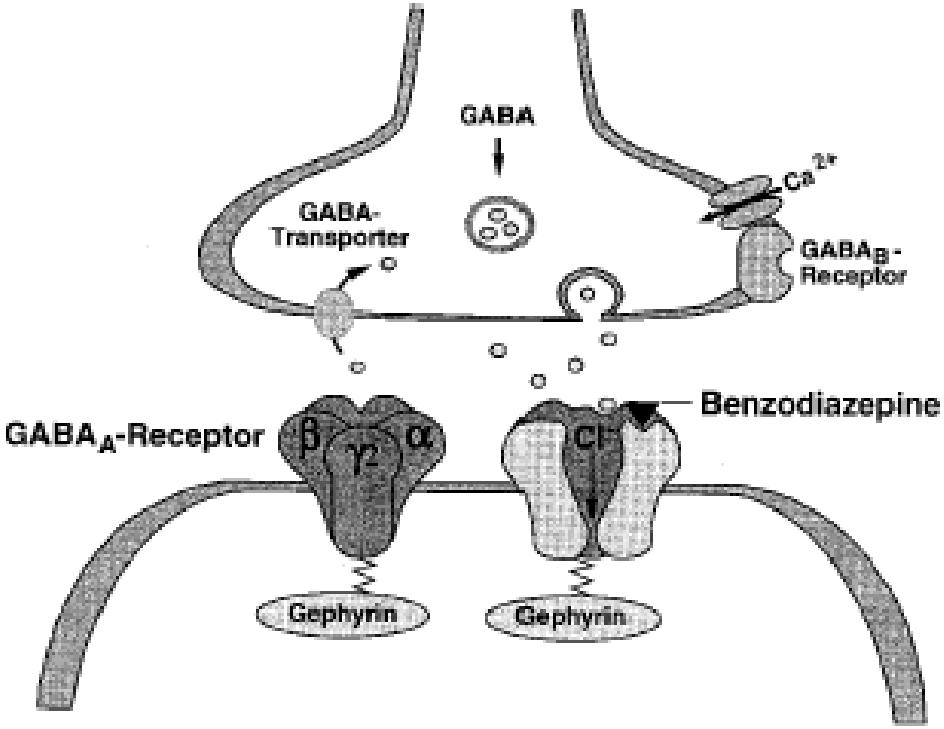
$GABA_A$ – BDZ Receptor Complex

α β γ subunits assemble in an uncertain stoichiometry to form a pentameric: GABA-$_A$ receptor





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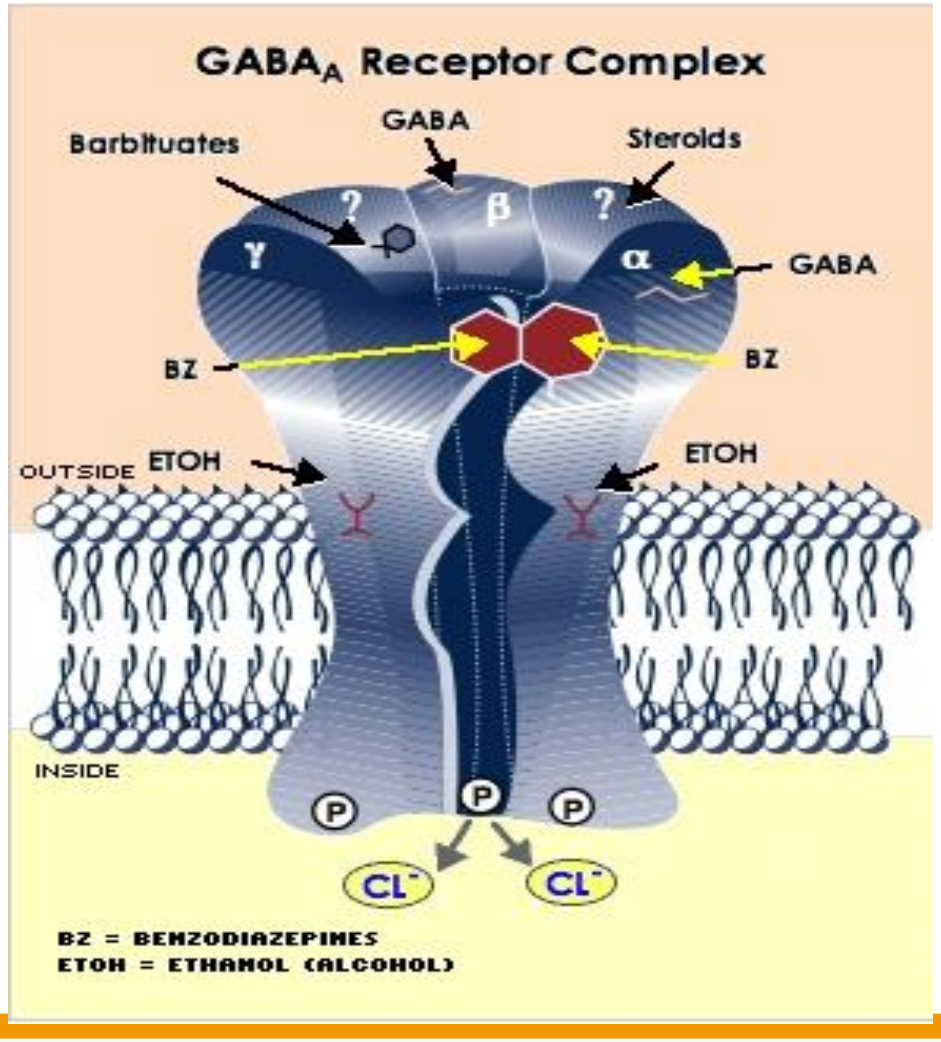
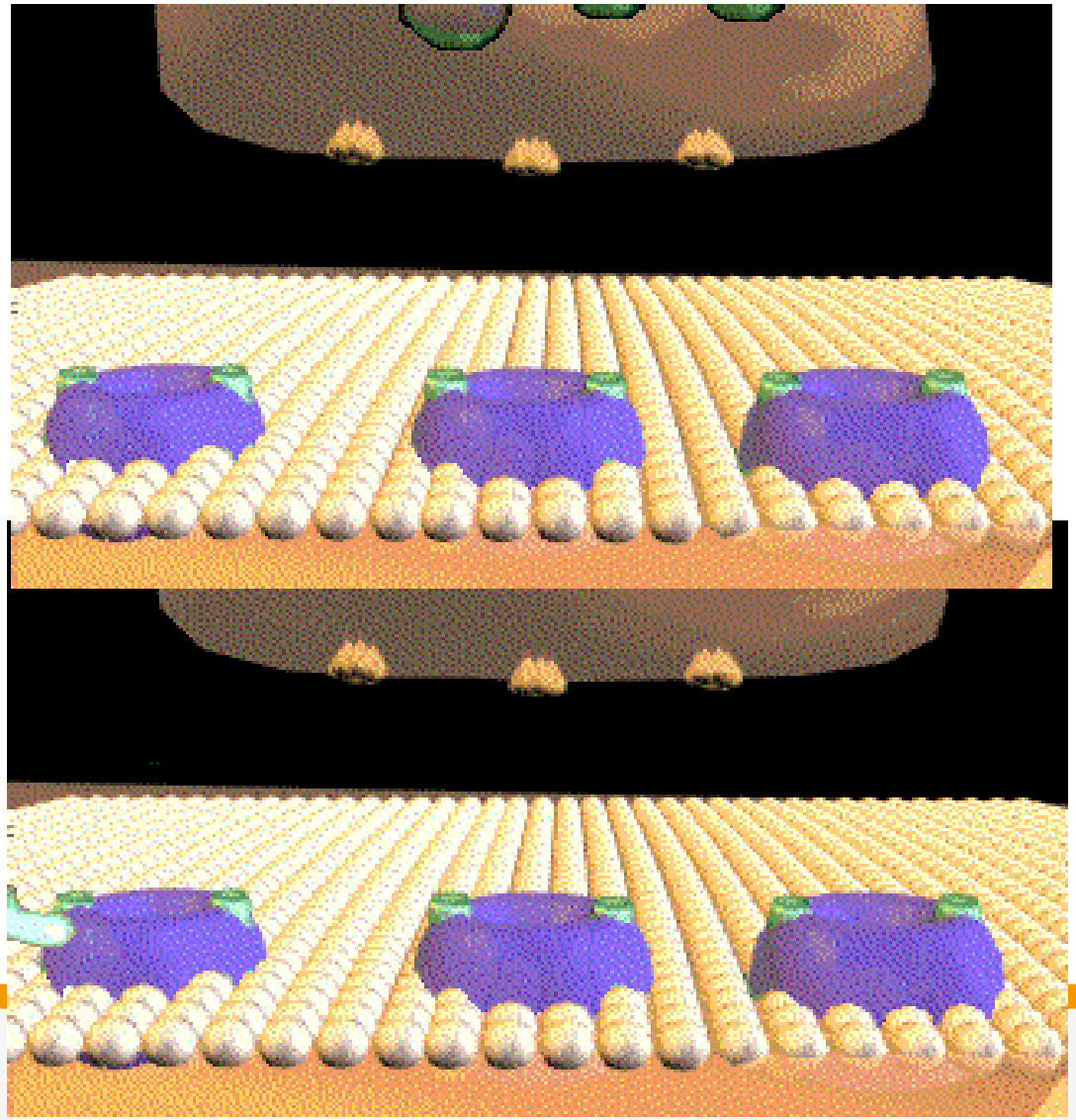
$GABA_A$ – BDZ Receptor Complex



BZD: Mechanism of Action



GABA

GABA receptor

Chloride channel

BZD

BZD do not directly gate GABA-A receptor/ion channel
(in contrast to Barbiturate)

Distribution of neurotransmitters

Acetylcholine (Ach)	• basal ganglia • cerebral cortex • basal nucleus of Meynert
Dopamine (DA)	• tuberoinfundibular (c.f. Prolactin secretion) • mesocorticolimbic (c.f. Schizophrenia) • nigrostriatal (c.f. Parkinson's) • ventral tegmental area
Serotonin (5-HT)	• brain stem - raphe nucleus, pons • cerebral cortex • limbic system
Noradrenaline (NA)	• brain stem - locus coeruleus • reticular activating system
GABA	• cerebral cortex • striato-nigral
Opiate (Op)	• periaquaductal grey matter
Glutamate (Glu)	• cortex and striatal pathways

Receptor	Subtype	Main actions of natural agonist	Drug Agonist	Antagonist
Adrenoceptor	α_1	• contraction of vascular smooth muscle • increased contractile force of the heart	ISOPROTENEROL, PHENYLEPHRINE	PRAZOSIN
	α_2	• contraction of vascular smooth muscle • reduced NA release	CLONIDINE	YOHIMBINE
	β_1	• increased contractile force of the heart	DOPAMINE, DOBUTAMINE	ATENOLOL, METOPROLOL
	β_2	• relaxation of smooth muscle	SALBUTAMOL	
Cholinergic	Muscarinic	heart rate, secretion, gut motility, broncho-constriction	PILOCARPINE	ATROPINE, BENZTROPINE, ORPHENADRINE, IPRATROPIUM
	Nicotinic	contraction of striated muscle		SUXAMETHONIUM, TUBOCURARINE
Histamine	H_1	broncho-constriction, capillary dilation		CHLORPHENIRAMINE, TERFENADINE
	H_2	↑ gastric acid		RANITIDINE, CIMETIDINE
Dopamine	D1-like (D_1, D_5) D_2-like (D_2, D_3, D_4)	CNS neurotransmitter	BROMOCRIPTINE	CHLORPROMAZINE, HALOPERIDOL, THIO-RIDAZINE
Opioid	μ (mu) δ (delta) κ (kappa)	CNS neurotransmitter	MORPHINE, PETHIDINE	NALOXONE
5-HT	5-HT_1 5-HT_{2A}, 5-HT_{2C} 5-HT_3			**Receptor**
GABA	$GABA_A$ $GABA_B$			**Subtypes**

Pharmacodynamics

Pharmacodynamics is the study of the mechanism of drug action

- "the effect of the drugs on the body"

Pharmacodynamics

Most psychoactive drugs affect the function of specific NTs either directly or indirectly

Drugs affecting monoamine NTs, DA, NA, 5-HT, are important in the treatment of psychotic and affective disorders

Drugs acting on amino acid NTs, GABA and glutamate are important in the treatment of anxiety disorders and epilepsy

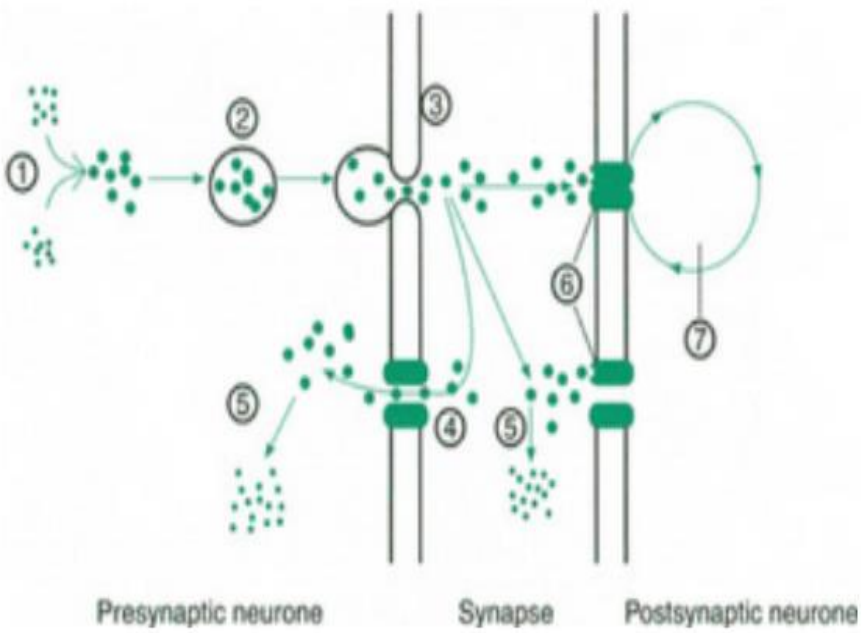
There is increasing interest in drugs acting on other NTs (e.g. peptides, nitric oxide)

Pharmacodynamics

Alteration of NT function is also commonly responsible for side effects (unwanted or adverse effects)

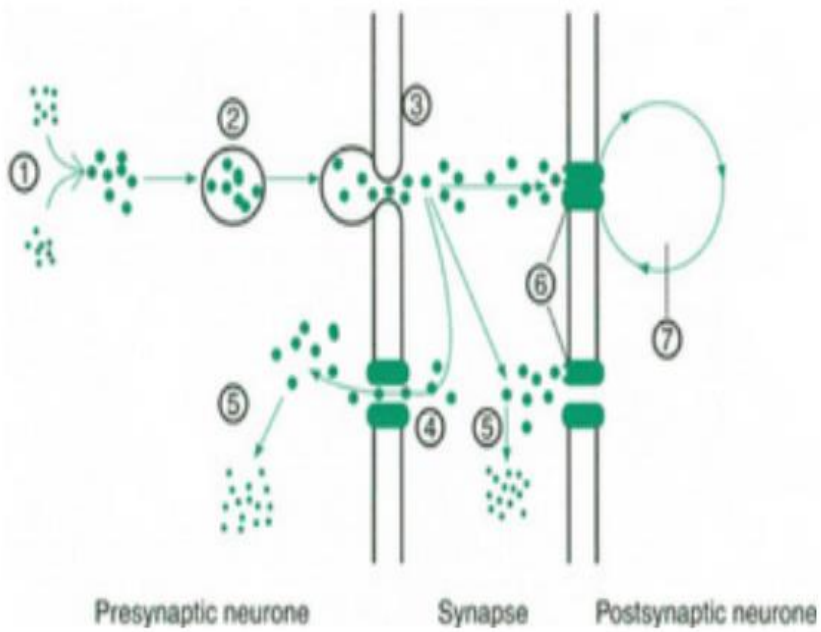
Drugs may also act at sites that directly alter neuronal function, e.g. alcohol

Sites of drug action on NTs



1. **Synthesis** (e.g. L-trytophan is the precursor of 5-HT and administration results in increased 5-HT synthesis)
1. **Storage** (e.g. reserpine depletes NA and DA stores in nerve terminal vesicles)
2. **Release** (e.g. amphetamine releases NA and DA into the synapse)
3. **Re-uptake** (e.g. TCAs inhibit monoamine re-uptake into the presynaptic neurone and so increase NT concentration in the synapse

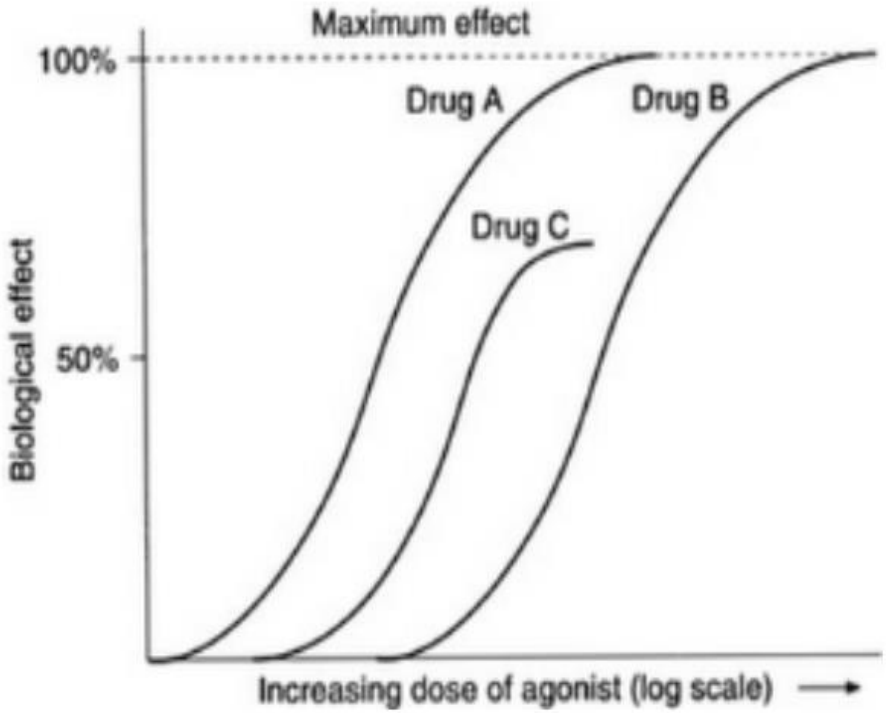
Sites of drug action on NTs



5. **Degradation** (e.g. monoamine oxidase inhibitors, MAOIs, prevent the breakdown of monoamine NTs).
6. **Receptors** (e.g. antipsychotics antagonise DA receptors).
7. **Other postsynaptic mechanisms** (e.g. lithium inhibits second messenger function, Ca2+ channel antagonists)

Agonists

- Agonists are drugs that mimic endogenous NTs.
- Most drugs bind reversibly to receptors and in the simplest case the response is proportiona to the fraction of receptors occupied (law of mass action).
- When maximum effects are achieved without full receptor occupance, there are said to be spare receptors



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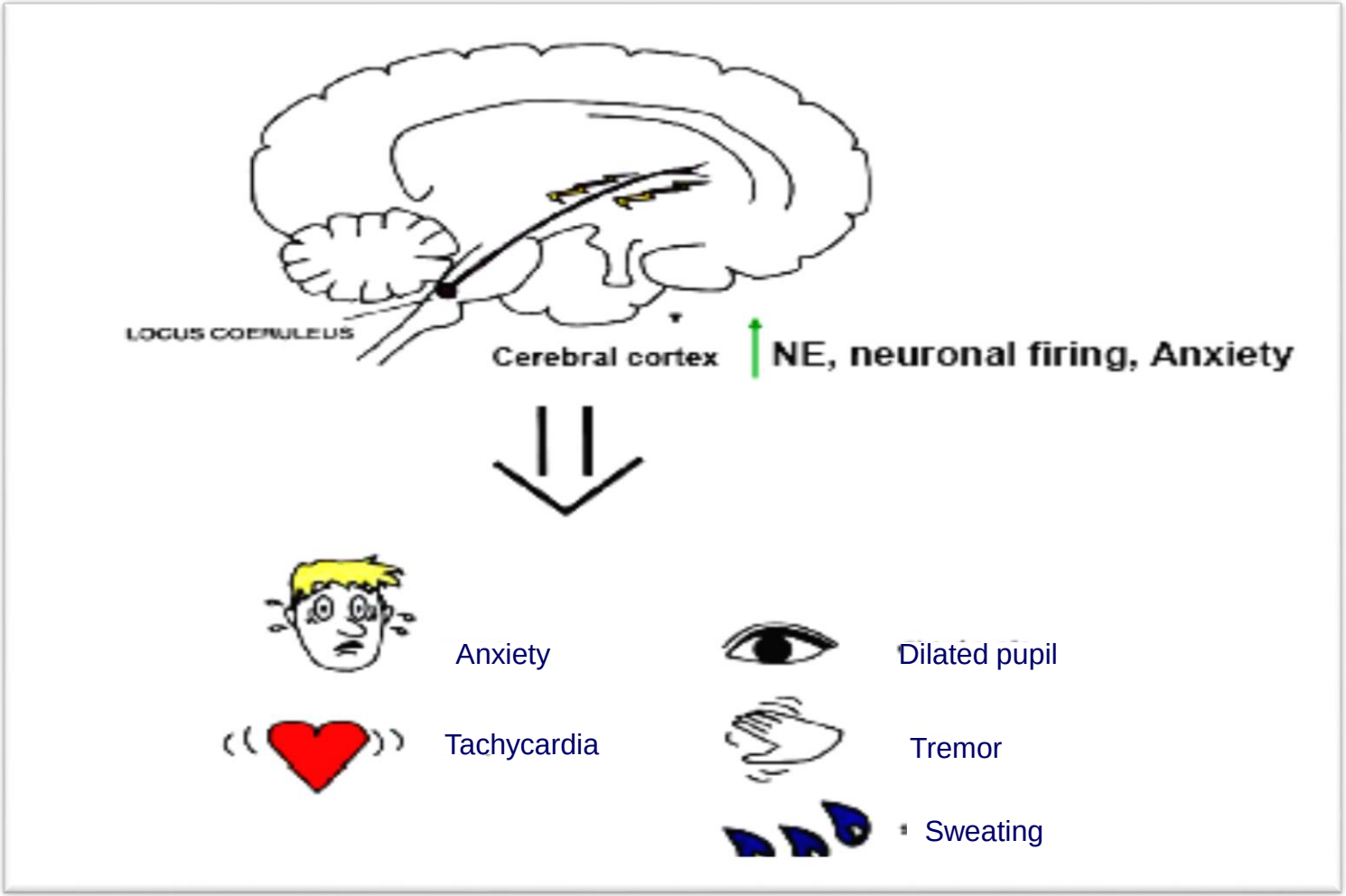
Overactivity of Norepinephrine Neurones



Alpha 2 agonist (clonidine)

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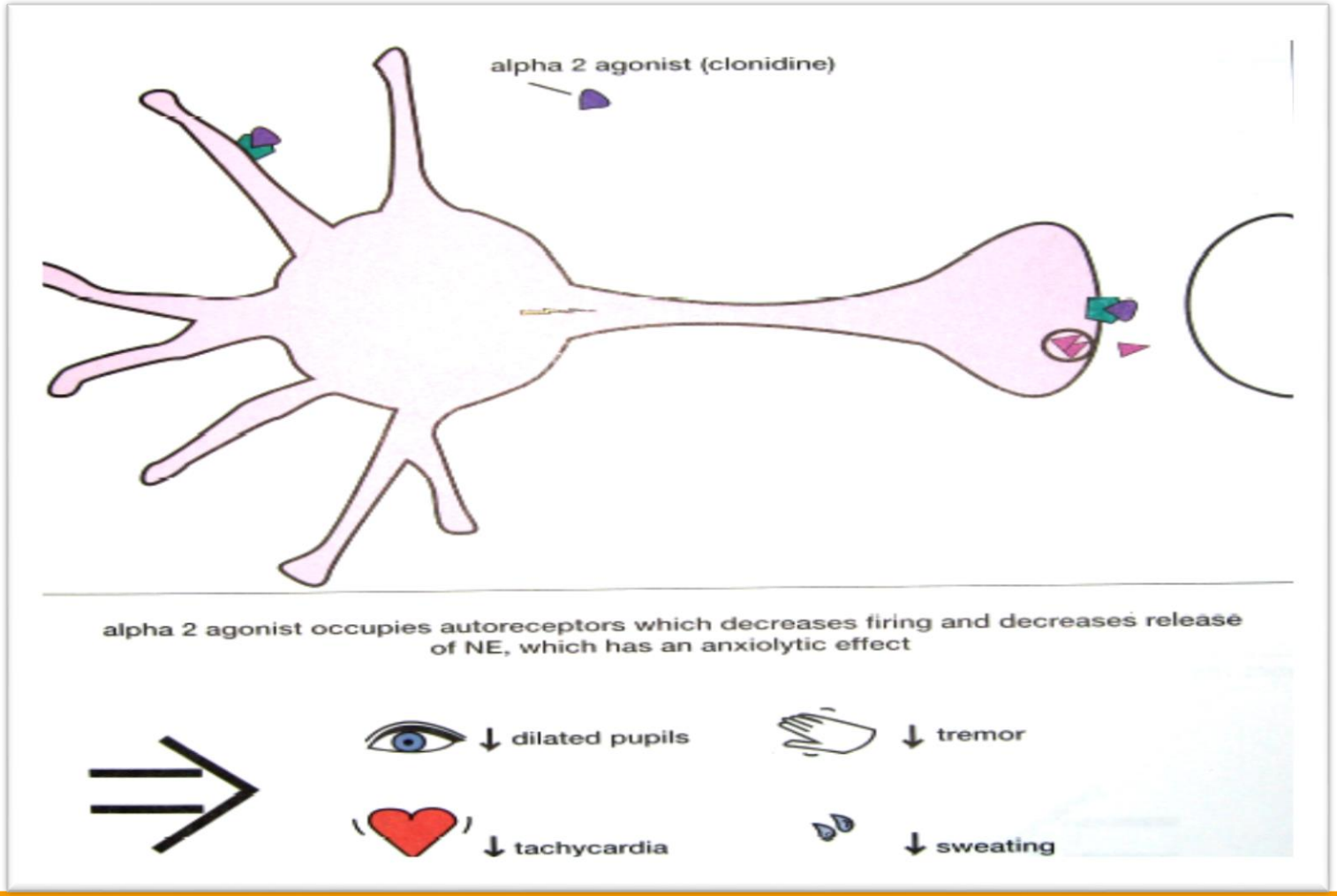
Alpha 2 agonist occupies autoreceptors which ↓ firing and ↓ release of NE,which has anxiolytic effect



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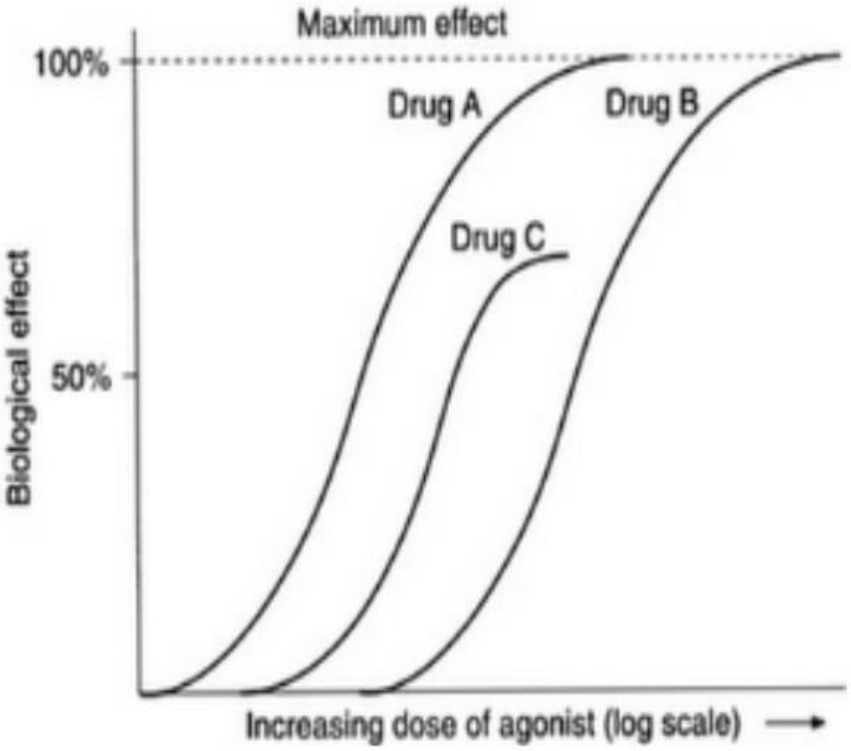
Agonists

- A&B bring about max responses, however A does so at a lower concentration than B (greater **affinity** for the receptor).
- C has a lower **efficacy** than A&B, and does not cause a maximal response, even when all the receptors are occupied, therefore is a **partial agonist**
- Partial agonists can partially antagonise the effect of the full agonist



5-HT1A Partial Agonists

5-HT1A partial agonists (buspirone, ipsapirone, gepirone) all have anxiolytic effects.

No affinity for BDZ receptors.

No sedation.

Not as effective as benzodiazepines, and exhibit delayed onset of therapeutic effect.

Metabolized by CYP3A4.

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5-HT1A Partial Agonists

Upregulate presynaptic auto-receptors (anxiolytic action) and postsynaptic heteroreceptors (nausea, dizziness) that mediate 5-HT activity.

Partial agonists, rather than full agonists. Partial agonists may act as agonists or antagonists, depending on the availability of endogenous 5-HT.

Slow onset of anxiolytic action (up to 3 weeks).

No sedation.

Principal adverse effects are nausea, GI upset, headache and dizziness.

5HT1A partial agonist causes up-regulation of autoreceptors (buspirone)

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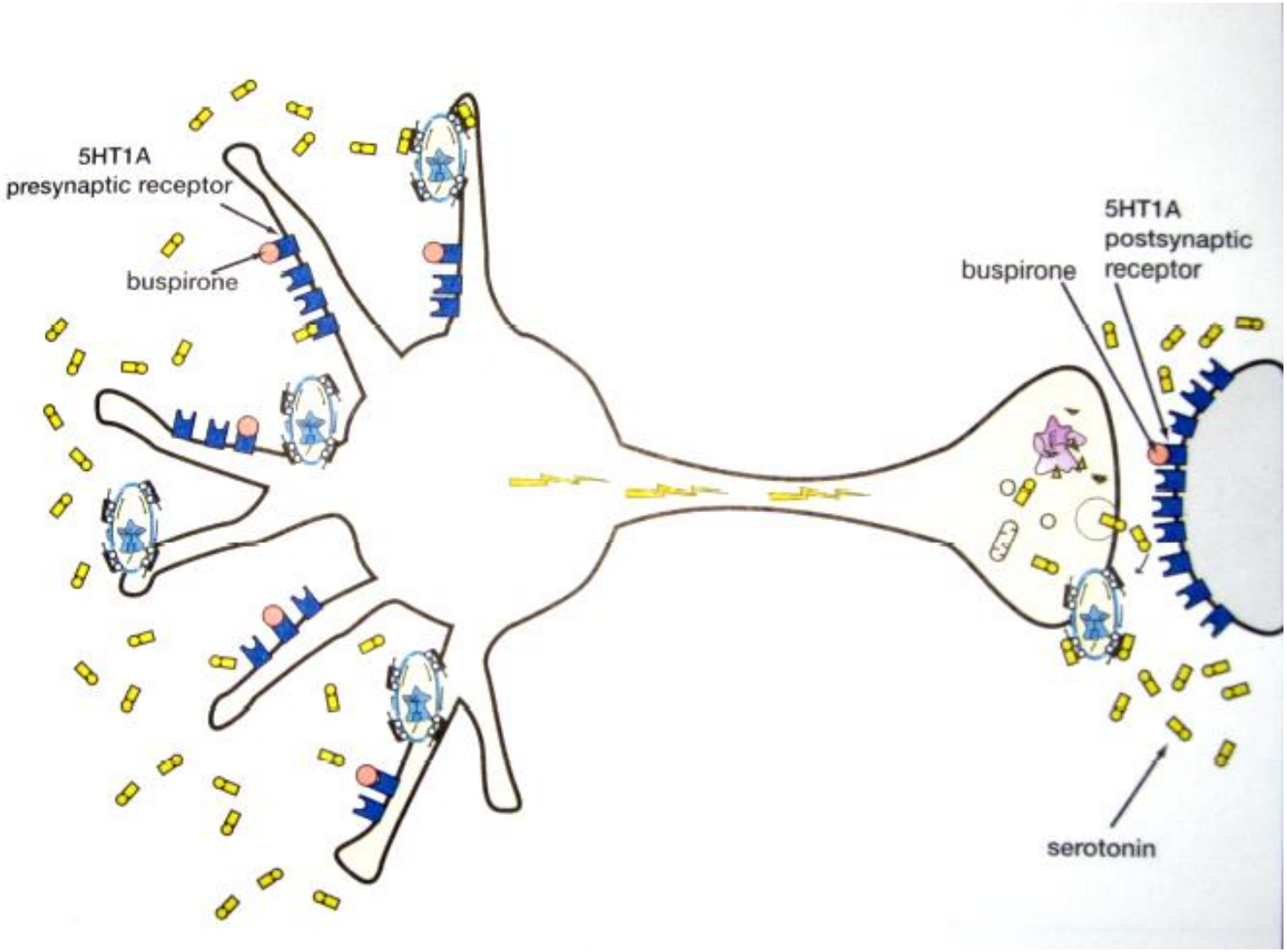


5-HT1A Partial Agonists: Buspirone

Rapidly absorbed in the gut, reaching peak plasma concentration within 1 hour.

Undergoes extensive first pass metabolism.

Active metabolite.

Plasma concentration is higher with food.

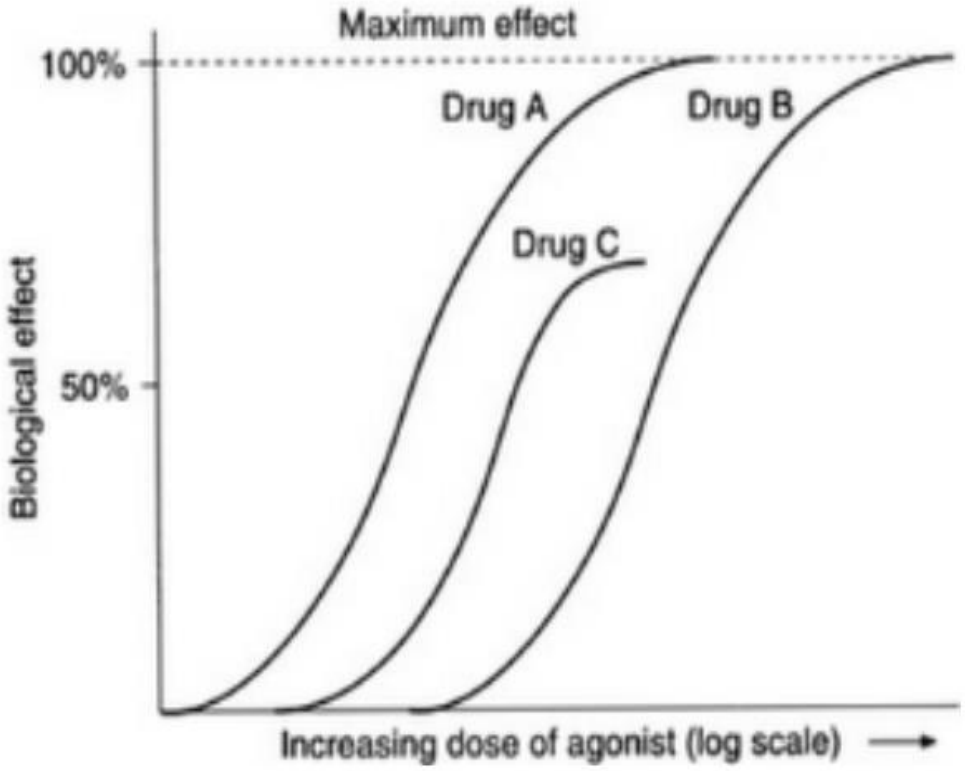
Elimination ½ life is 3 hours (slow release 9 hrs).

No pharmacological dependence.
No sedation, no interaction with alcohol
S/E are nausea, GI upset, headache and dizziness

Agonists

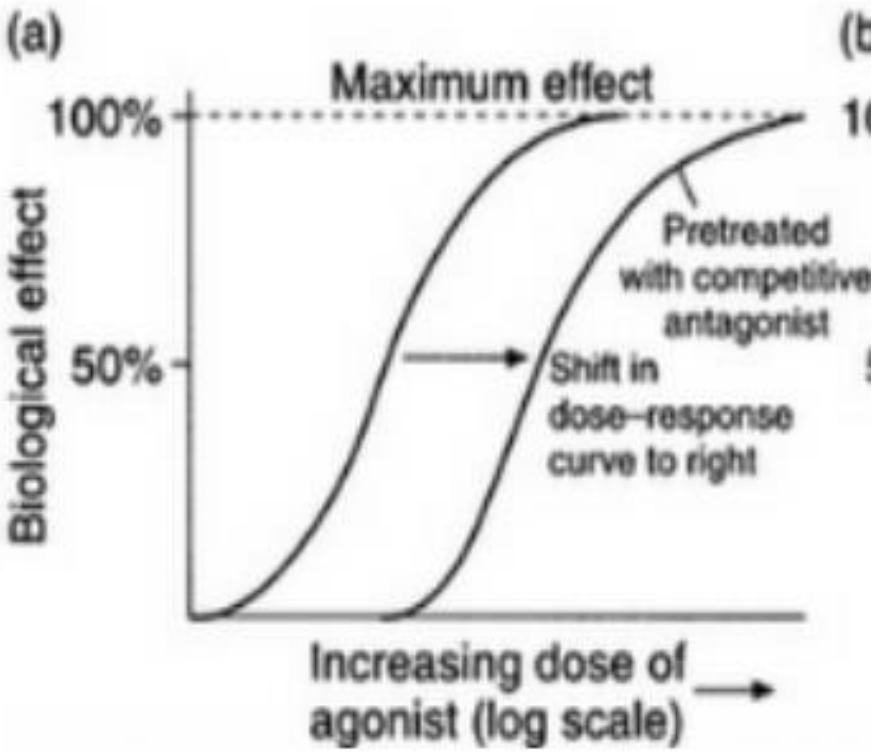
The **potency** of a drug is determined by:

- The proportion of the drug reaching the receptor;
- Its affinity for the receptor
- Its efficacy



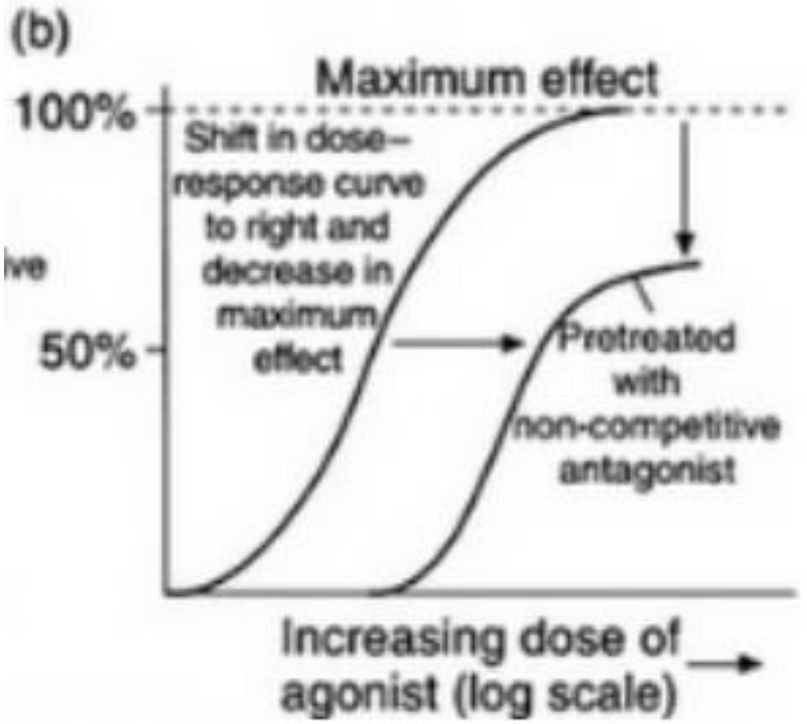
Antagonists

- Antagonists bind to receptors without causing an effect and they block the action of (shift to the right in the dose response curve for the agonist)
- Most antagonist drugs are competitive and are displaced from their binding sites by agonists so that at high doses the agonist can still exert max effect.
- This competition is influenced by the relative affinity of the agonist and antagonist for the receptor.



Antagonists

- Non competitive antagonists cannot be displaced by agonists and not only shift the curve to the right, but also reduce the max effect.
- Noncompetitive antagonists may be reversible if the system is restored to normal, when the antagonist is removed, or irreversible if restoration of function requires synthesis of new receptors.



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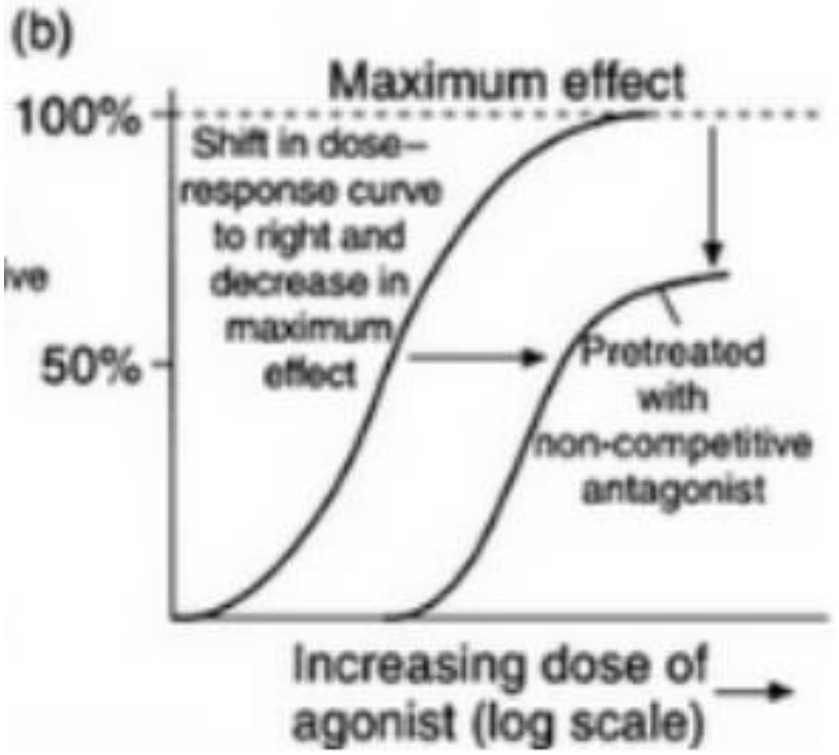
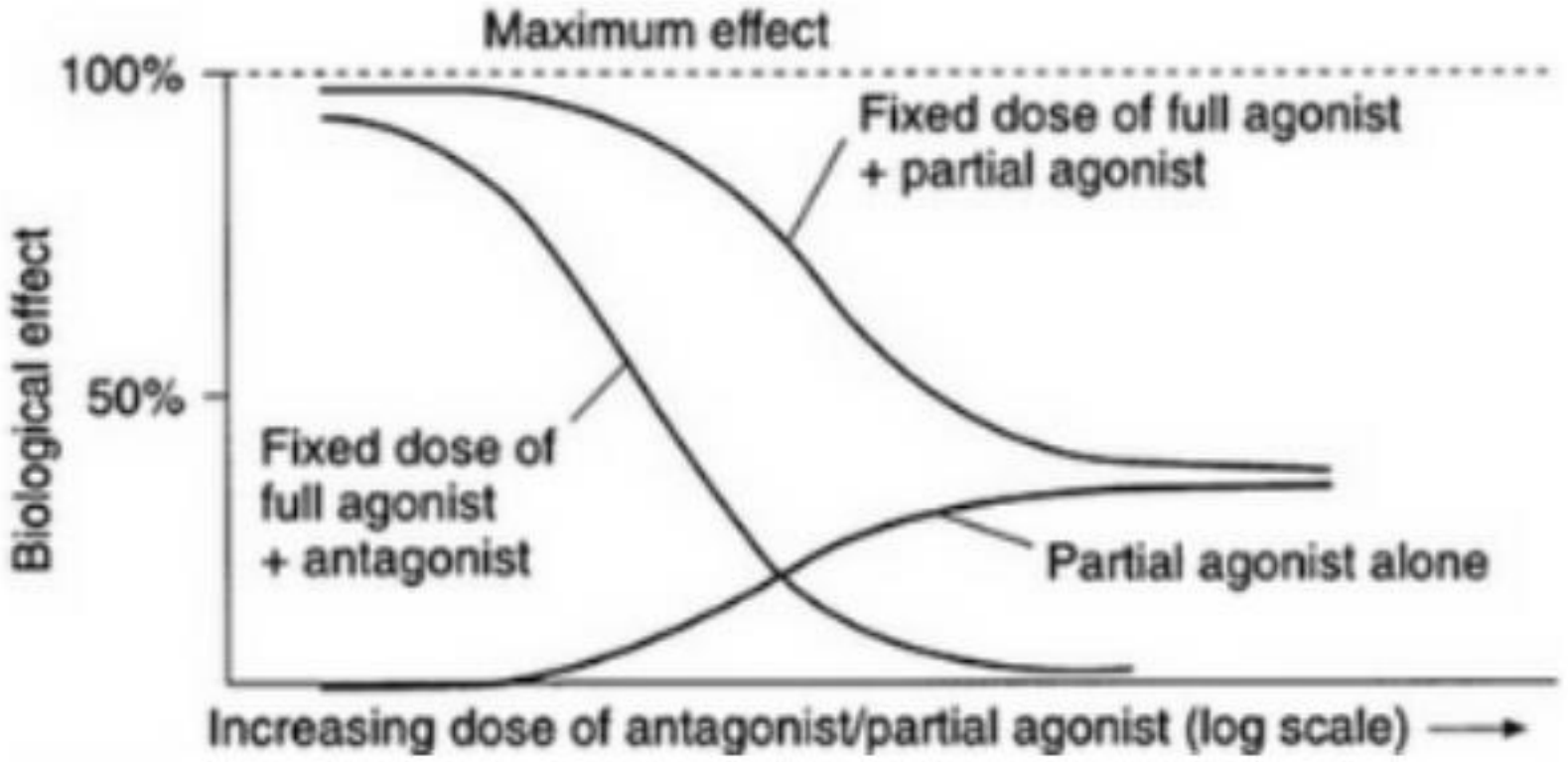


Antagonists



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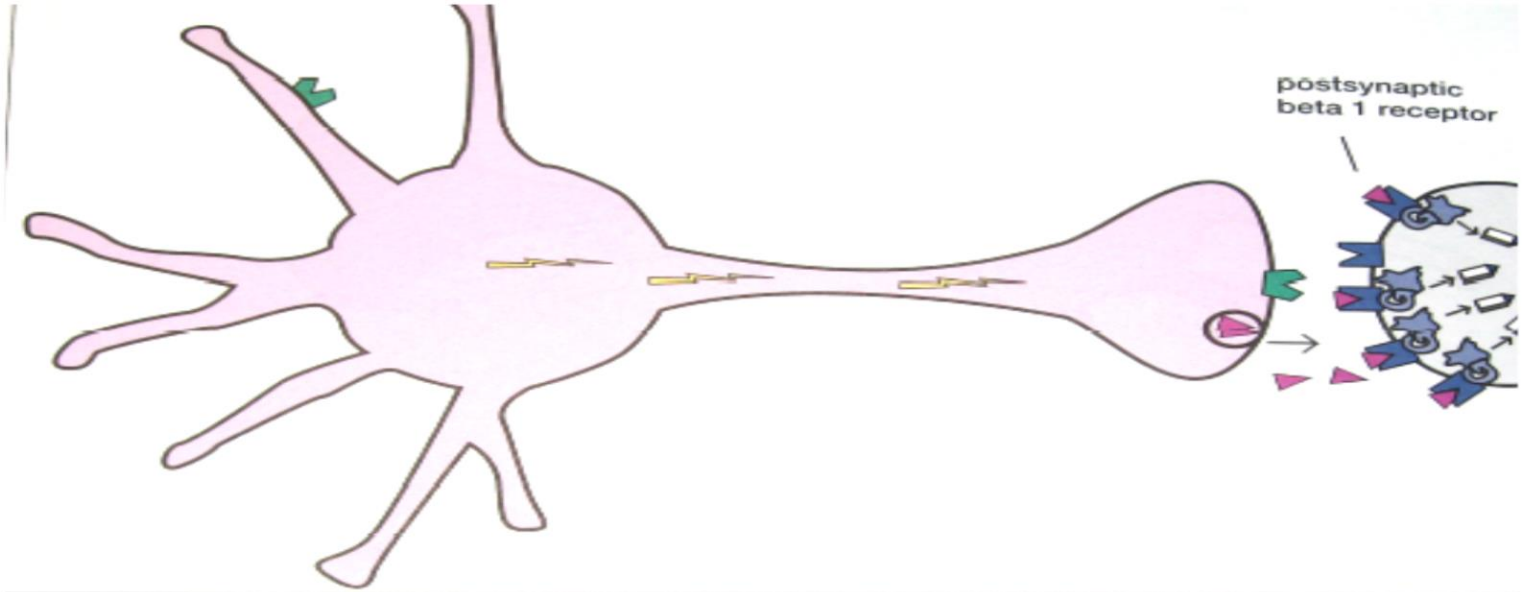
Post Synaptic Beta Adrenergic Activity



Overactivity at the postsynaptic beta receptors increases anxiety

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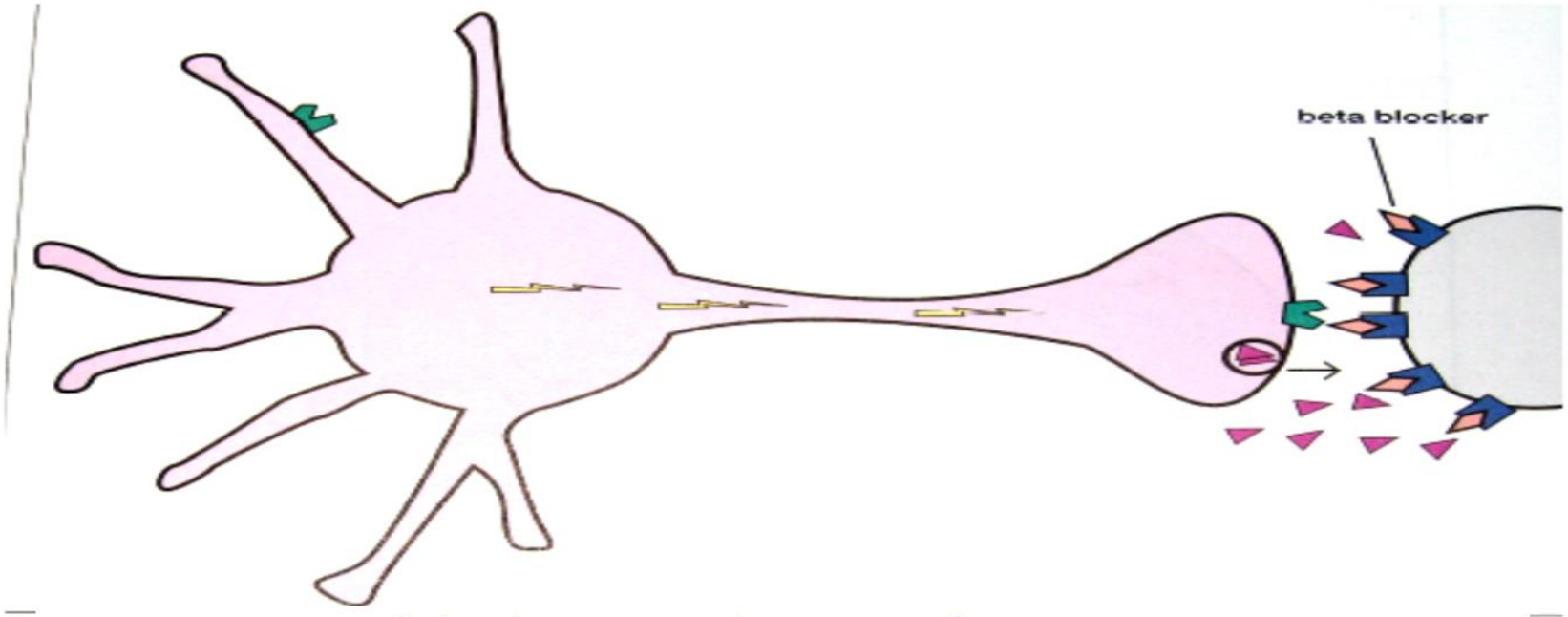
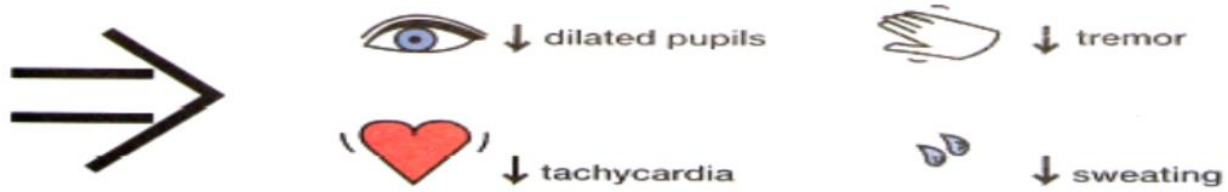
Beta-adrenoreceptor Antagonists (e.g. Propranolol)



Blocking the postsynaptic beta receptors decreases anxiety



Beta-adrenoreceptor Antagonists: (e.g. Propanolol)

Sometimes used to treat peripheral sympathetic responses to anxiety (such as tremor, palpitations, etc.) rather than to treat any CNS symptoms

Effects on peripheral beta receptors

Could be useful in certain situations, such as stage fright

Propranolol may attenuate symptoms of BDZ withdrawal

Side effects: hypotension, lethargy, impaired concentration and sleep disturbance/ nightmares /depression

Tolerance and sensitisation

Tolerance describes the diminished response to the administration of a drug after repeated exposure. It may be caused by:

- Increased metabolism (e.g. carbamazpine increased the activity of enzymes that metabolise it: enzyme induction);
- Reduced receptor sensitivity or number (downregulation)
- Activation of a homeostatic mechanism (e.g. in the second messenger or effector system);
- Behavioural tolerance through learning to cope with effects

Tolerance and sensitisation

Cross-tolerance between drugs is the basis for a number of drug interactions:

- Alcohol with barbiturates
- Carbamazepine with OCP

Sensitisation is the enhancement of drug effects following the repeated administration of the same dose of drug

- Stimulants such as amphetamines in animals

Benzodiazepines

Benzodiazepines

Most commonly prescribed anxiolytic and hypnotic drugs

BDZ increase the affinity of the $GABA_A$ receptor for GABA (increase ***frequency*** of Cl channel opening)

First identified in 1957
Taming effect on test animals
Chlordiazepoxide 1961, diazepam 1962

Less potent and fewer problems than barbiturates
Type 1 – mainly cerebellum (anxiolytic, sedative & hypnotic)
Type 2 – mainly limbic region (anticonvulsant)

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Pharmacological Actions Of Benzodiazepines

Reduction of anxiety

Sedation and induction of sleep

Reduce REM sleep and slow wave sleep

Anticonvulsant effect

Reduction of muscle tone and coordination (independent of sedation)

BZD: INDICATIONS

Insomnia :

All BZD hypnotic
Ideal hypnotic:
Rapid onset at bedtime,
sustained action to facilitate sleep throughout night
no residual morning effect

Short acting agents like Triazolam (t1/2 ~3 h) fits this but rebound insomnia upon discontinuance, with careful selection of dosages long acting Flurazepam (t1/2 ~70 h) more effective

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BZD: INDICATIONS

Anxiety:

All BZD have some anxiolytic
Chlordiazepoxide, Diazepam, Oxazepam, Lorazepam, Alprazolam

Anti-convulsant: Clonazepam, Diazepam, clobazam

Skeletal muscle relaxant: Diazepam

Pre-anaesthetic medication: Diazepam, Midazolam

Alcohol withdrawal: Chlordiazepoxide

Pharmacokinetic Properties Of Diazepam

Bioavailability	Almost complete after oral dosing
Peak conc.. (single dose)	30-90 minutes
Protein binding	95%
Renal excretion	Negligible
Metabolism	*Phase I* to active metabolite *Phase II* for inactivation
Elimination half life **-Young adults** **-Elderly** **-Desmethyldiazepam**	 20 hours 30-100 hours 30-90 hours

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Adverse Effects Of Diazepam

Common

- Drowsiness & dizziness
- Psychomotor impairment

Occasional

- Dry mouth & blurred vision
- GI upset
- Ataxia & headache
- Reduced BP

Rare

- Amnesia & restlessness
- Skin rash

BZD: ADVERSE EFFECTS

- Impaired psychomotor performance
  - Increased reaction times / Motor incoordination
- Confusion
- Residual day time sleepiness
- Sometimes bizarre behaviors
- Paradoxical effects
- Abuse potential: Dependence
  - Low as compared to barbiturates but may be serious on chronic use

N.B. In overdose – effects can be reversed by Flumazenil

Pharmacokinetic Properties of Benzodiazepines in Humans

NHS
Health Education England

Drug	Peak Blood Level (Hours)	Elimination Half-Life[1] (Hours)	Comments
alprazolam	1-2	12-15	Rapid Oral Absorption
chlordiazepoxide	2-4	15-40	Active metabolites; erratic bioavailability from IM injection
clorazepate	1-2 (nordiazepam)	50-100	prodrug; hydrolyzed to active form in stomach
diazepam	1-2	20-80	Active metabolites; erratic bioavailability from IM injection
estazolam	2	10-24	No active metabolites
flurazepam	1-2	40-100	Active metabolites with long half-lives

[1] *Includes half-lives of major metabolites*

Pharmacokinetic Properties of Benzodiazepines in Humans

NHS Health Education England

Drug	Peak Blood Level (Hours)	Elimination Half-Life[1] (Hours)	Comments
lorazepam	1-6	10-20	
oxazepam	2-4	10-20	No active metabolites
prazepam	1-2	50-100	Active metabolites with long half-lives
quazepam	2	30-100	Active metabolites with long half-lives
temazepam	2-3	10-40	Slow oral absorption; no active metabolites
triazolam	1	2-3	No active metabolites

[1] *Includes half-lives of major metabolites*

Tolerance to Benzodiazepine Effect

Easily studied in animals

- Initially decrease in exploratory behaviour and general motor activity
- Tolerance to this and muscle relaxant, anticonvulsant properties and anxiolytic effects.
- In humans, tolerance to sedative and anticonvulsant effect in 2-3 weeks
- ? Tolerance to desirable anxiolytic and hypnotic effects
- Cross tolerance

Mechanisms For Tolerance?

Pharmacokinetic factors

- Induction of metabolism or less active metabolites
- More imp in barbiturates & alcohol

Pharmacodynamic factors

- Reduction in BDZ receptors and/or sensitivity with ch. Treatment
- Uncoupling of links b/w BDZ and $GABA_A$ receptor

Cognitive theories

- Organisms learning new responses

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Benzodiazepine Withdrawal Symptoms

Anxiety Symptoms	Disturbance of Perception	Rare effects (severe)
Anxiety	Hypersensitivity to perception	Paranoid psychosis
Dysphoria	Abnormal bodily sensations	Depressive episode
Tremors	Abnormal sense of movement	Seizures
Muscle pains	Depersonalisation	Confusion
Sleep disturbance	Visual disturbance	Hallucinations
Headache		
Nausea, anorexia		
Sweating		
Fatigue		

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Benzodiazepines :Potential Drug-Drug Interactions

- CNS depressants including alcohol **– enhancement effects**
- Smoking & caffeine **– decrease effect**
- SSRIs, grapefruit juice **inhibit CYP3A4 and increase BZD levels**
- **Benzodiazepine receptor antagonists –** flumazenil
  - Used to counteract adverse effects of BDZ
  - Rapid onset and short duration
  - May precipitate seizures, arrhythmias, emotional lability

Barbiturates

Non selective CNS depressants

Enhanced GABA transmission

Also alter gating mechanism of Cl channels (increase duration of opening)

Once main stay anxiolytic and hypnotic drugs (1903/1912)

Now mainly in anaesthesia and Rx of epilepsy (phenobarb.)

Respiratory and cardiovascular depression leading to death on over dose

Why Benzodiazepines Are Safer Than Barbiturates?

Barbiturate overdose is much more dangerous

- Respiratory depression – irreversible pharmacologically

Benzodiazepines produce less severe drug tolerance and dependence

The benzodiazepine competitive antagonist flumazenil can be used to treat benzodiazepine overdose

All barbiturates are potent inducers of the cytochrome P450 system, and cause drug interactions

Antidepressant Drugs

SSRI often used in management of anxiety disorder as well as depressive disorders.

Paroxetine, sertraline, citalopram, escitalopram

Both SSRIs and 5-HT1A partial agonists show delayed onset of their therapeutic effects, suggesting that secondary adaptive responses in the 5-HT and related systems are responsible for therapeutic efficacy.

Clomipramine and imipramine in PD.

Venlafaxine in GAD.

Selective Benzodiazepine Ligands

(Do not alter stages of sleep)

Zolpidem & Zaleplon

- BZD type 1 receptor (α-1 subunits)
- Potent hypnotics and less psychomotor impairment
- Very short half life (1-2 hrs)
- S/E headache, nausea & dizziness

Zopiclone

- Binds $GABA_A$-BDZ complex BUT at different site
- Half life of 3-4 hrs
- Tolerance, rebound insomnia after 3 weeks
- Psychomotor impairment
- S/E headache, nausea & dizziness

Other Drugs

Chloral hydrate

- Not widely used, occ. as hypnotics
- Tolerance and dependence as in BDZ
- Toxic in O/D esp. with alcohol

Paraldehyde

- In 1882 as hypnotic
- Minimal use, as a last resort in rapid tranquilisation
- Drowsiness and respiratory depression

Antipsychotics

Melatonin

Orexin antagonist……. (orexin receptor mediates wakefulness)