Biological Therapy in Psychiatry

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Mental Health Care Pre-1930's

Before we begin…

"It should be made clear that all psychotropic drugs can be safe or harmful, depending on the circumstances in which they are used, how frequently they are used, or how much is used."
Grilly (2002), *Drugs and Human Behavior*

What is a ‘drug’?

- A very vague term
- all ingested substances alter bodily function
- ‘drug’ is reserved for things that have pronounced effects when ingested in small quantities

HISTORY OF ANTIPSYCHOTICS

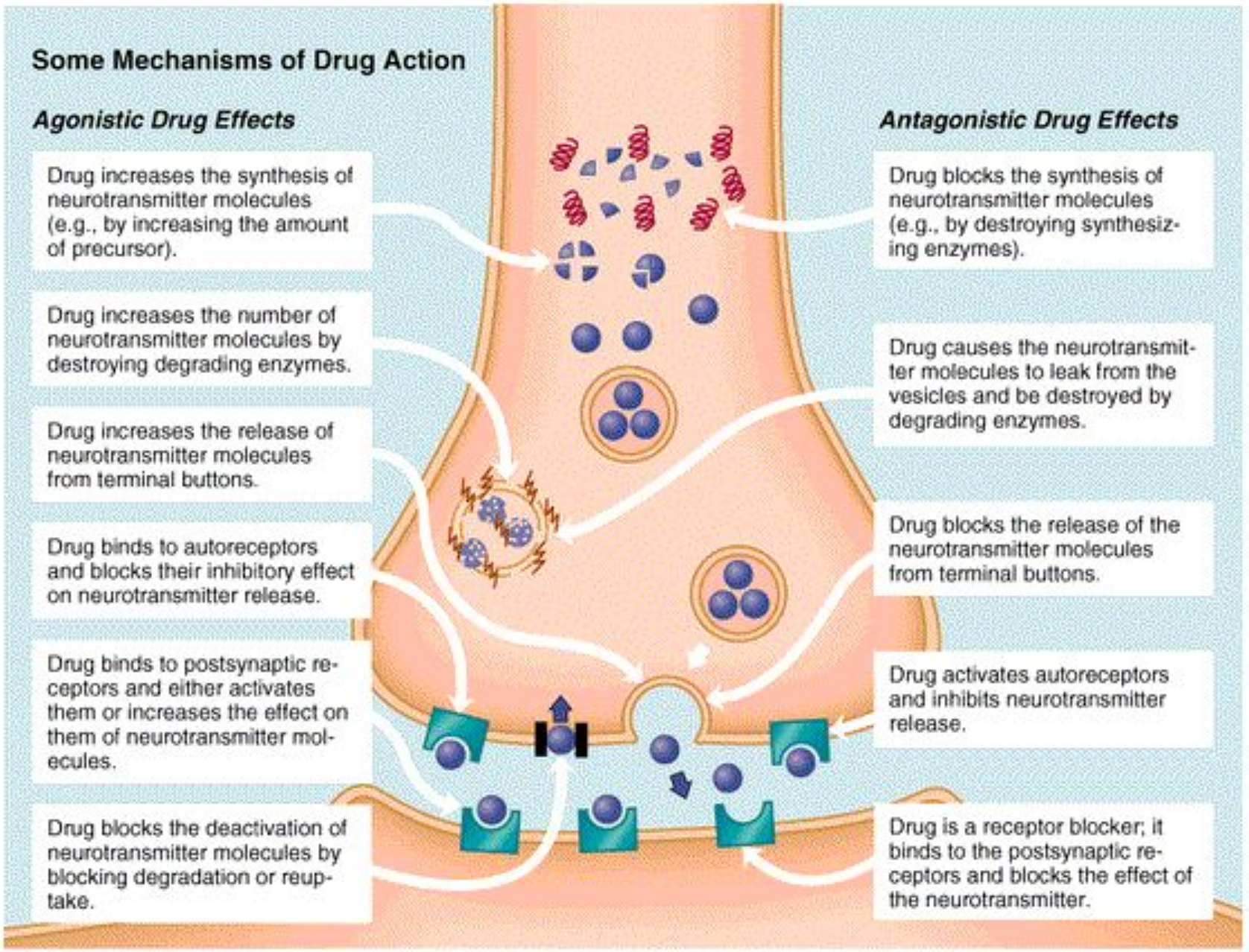
- Anti-psychotics were discovered accidentally by a French naval surgeon, Henri Laborit. Laborit was interested in circulatory shock, not schizophrenia.
- Laborit experimented with a variety of drugs to combat shock syndrome.
- One of the drugs was an agent called Promethazine. His primary reason for using the drug was for its effects on the ANS(autonomic) , however, he discovered the secondary properties of the drug
  - The drug made patients drowsy, reduced pain, and created a feeling of euphoric quietude." This drug has psychological effects.
- Laborit's observation were used to modify the formula of Promethazine into the first effective anti-psychotic medication, Chloropromazine (Thorazine).

Heinrichs, R. W., (2001). In Search of Madness: Schizophrenia and Neuroscience. Oxford University Press: New York.

Treatment Before Drugs Came into Play

- King Saul – vine, music-therapy
- Patients were kept isolated from everybody else.
- Shock Treatment: consisted of twirling patients on a stool until they lost consciousness or dropping them through a trap door into an icy lake
- Insulin-Shock Therapy: consisted injecting insulin into the patient until he or she became hypoglycemic enough to lose consciousness and lapse into a coma
- Institutionalized

► Mechanisms of Drug Effects



Efficacy and Potency

- Efficacy - Ability of a drug to produce a response as a result of the receptor or receptors being occupied.
- Potency - Dose required to produce the desired biologic response.
- Loss of effect
  - desensitization (rapid decrease in drug effect)
  - tolerance (gradual decrease in the effect of a drug at a given dose)
  - can lead to being treatment refractory

Drug Toxicity

- Toxicity: Point at which concentrations of the drug in the blood stream become harmful or poisonous to the body.
- Therapeutic index: Ratio of the maximum nontoxic dose to the minimum effective dose.
  - High therapeutic index: Wide range between dose at which the drug begins to take effect and dose that would be considered toxic.
  - Low therapeutic index - low range

Absorption

- From site of administration into the plasma
- Oral - (tablet and liquid) (Table 8-3)
  - Most Convenient
  - Most variable (food and antacids)
    - First pass effect
    - Decreased Gastric Motility (age, disease, medication)
- IM - Short-and long acting
- IV - Rarely used

Pharmacokinetics: How the Body Acts on the Drug

- Absorption
- Distribution
- Metabolism
- Elimination

Bioavailability

- Amount of drug that reaches systemic circulation unchanged

- Often used to compare one drug to another, usually the higher the bioavailability, the better.

Distribution

- Amount of drug found in various tissues, especially the intended ones.
- Psychiatric drugs must pass through blood-brain barrier (most fat-soluble)
- Factors effecting distribution
  - Size of organ (larger requires more)
  - Blood flow (more, greater concentration)
  - Solubility (greater, more concentration)
  - Plasma Protein (if bound, slower distribution, stays in body longer)
  - Anatomic Barriers (tissues surrounding)

Crossing the Blood Brain Barrier

- Passive diffusion
  - Drug must dissolve in the structure of the cell
  - Lipid solubility is necessary for drugs passing through blood brain barrier (then, can also pass through placenta)
- Binding to other molecules
  - Plasma protein binding
  - The more protein binding, the less drug activity.
  - Can bind to other cells, especially fat cells. Then are released when blood level decreases.

Metabolism

- Process by which the drug is altered and broken down into smaller substances (metabolites) that are usually inactive.
- Lipid-soluble drugs become more water soluble, so they may be more readily excreted.
- Most metablism is carried out in the liver.

Elimination

- Clearance: Total amount of blood, serum, or plasma from which a drug is completely removed per unit time.
- Half-life: Time required for plasma concentrations of the drug to be reduced by 50%.
- Only a few drugs eliminated by kidneys (lithium)
- Most excreted in the liver
  - excreted in the bile and delivered to the intestine
  - may be reabsorbed in intestine and "re-circulate" (up to 20%)

Dosing and Steady State

- Dosing: Administration of medication over time, so that therapeutic levels can be achieved.
- Steady-state:
  - drug accumulates and plateaus at a particular level
  - rate of accumulation determined by half life
  - reach steady state in about five times the elimination half-life

Pharmacokinetics: Cultural Considerations

- 9% of whites - genetically defective P-450_{2D6}
- Asian descent
  - Metabolize ethanol to produce higher concentrations of acetaldehyde (flushing, palpitations)
  - Require 1/2 to 1/3 dose antipsychotics and more severe side effects
- Cardiovascular effects of propranolol
  - Asian descent - more sensitive
  - African descent - less sensitive

Phases of Drug Treatment

- Initiation
- Stabilization
- Maintenance
- Discontinuation

Tolerance & Dependence

- Tolerance – state of decreased sensitivity to the drug as a result of exposure to it.
  - functional tolerance (number of
  - binding sites is reduced – also called
  - "down regulation" of receptors)
  - note: opposite phenomenon: up-regulation
- Physical Dependence – caused by withdrawal symptoms (not the reason that people continue to take most drugs)
- Psycholological Dependence (now called positive-incentive theory of addiction)

Receptors

- **Types of Action**
  - **Agonist: same biologic action**
  - **Antagonist: opposite effect**
- **Interactions with a receptor**
  - **Selectivity: specific for a receptor**
  - **Affinity: degree of attraction**
  - **Intrinsic activity: ability to produce a biologic response once it is attached to receptor**

Ion Channels

- **Drugs can block or open the ion channels**
- **Example: benzodiazepine drugs facilitate GABA in opening the chloride ion channel**

Enzymes

- Enzymes catalyze specific biochemical reactions within cells and are targets for some drugs.
- Monoamine oxidase is an enzyme that breaks down most bioamine neurotransmitters (NE, DA, 5-HT).
- Enzymes may be inhibited to produce greater neurotransmitter effect.

Carrier Proteins

- **Transport neurotransmitters across cell membranes**
- **Medications may block or inhibit this transport.**
- **Example: antidepressants**

Being a neurotransmitter: What does it take?

- Exists presynaptically
- Synthesis enzymes exist presynaptically
- Released in response to action potential
- Postsynaptic membrane has receptors
- Application at synapse produces response
- Blockade of release stops synaptic function

Neurotransmitters

80 plus chemical substances that provide communication between cells. Some of these are actually NTs and others are neuromodulators (i.e. they augment the activity of the NT)

Drug Effects on Neurotransmission

- All psychoactive drugs act centrally (i.e. on the brain)
- The vast majority of drug actions are through direct effects on neurotransmission
  - Agonist
    - A drug that activates the same receptors as a neurotransmitter
  - Antagonist
    - A drug that blocks receptors activated by a neurotransmitter
  - Indirect agonist
    - A drug that increases the availability of a neurotransmitter
  - Inverse agonist
    - Only happens at complex receptor types
    - Drug activates the receptor, but has the *opposite* effect as the endogenous ligand (neurotransmitter)
  - Mixed agonist-antagonist
    - Drug acts as an agonist, but blocks the effects of other agonists

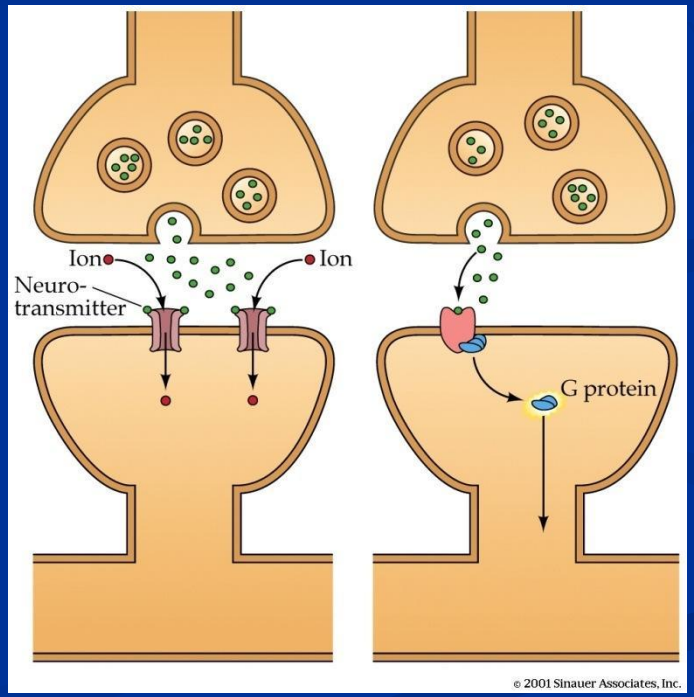
Neurotransmitters have 7 actions

1. Synthesized
2. Stored
3. Enzymatically destroyed if not stored
4. Exocytosis
5. Termination of release via binding with autorecptors
6. Binding of NT to receptors
7. NT is inactivated

Drugs are developed that address these actions as an AGONIST (mimic the NT) or ANTAGONIST (block the NT)

A quick review of synaptic action

- receptor types (ionotropic and metabotropic)
- receptor subtypes



Metabotropic receptor

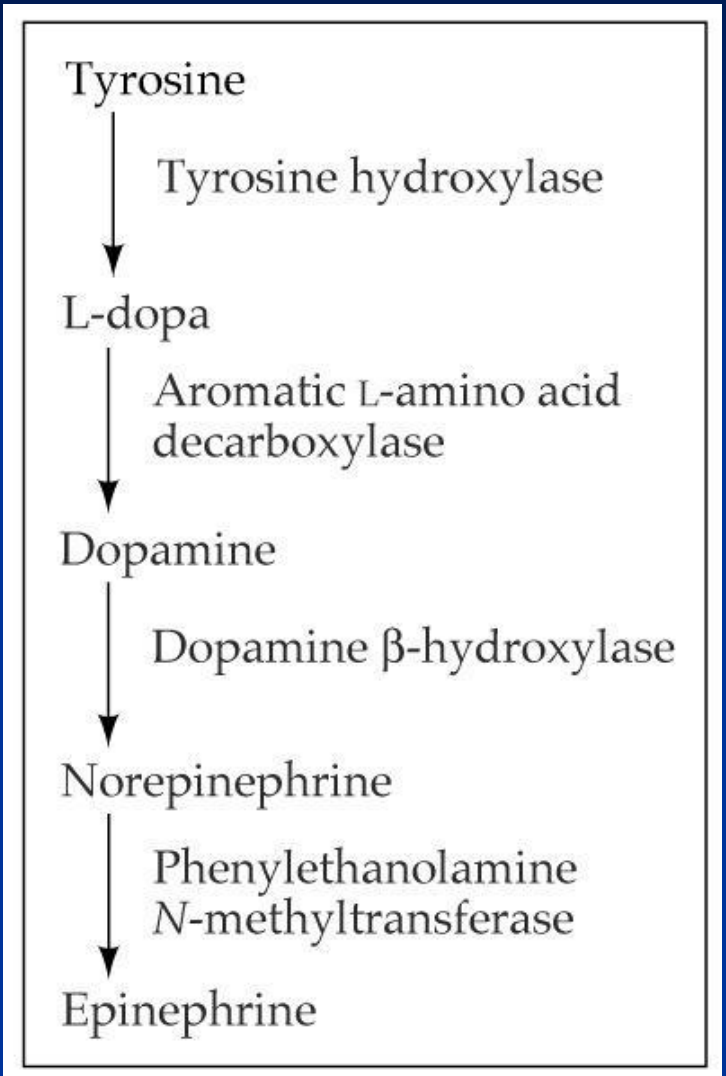
- Includes the metabotropic **glutamate** receptors, **muscarinic acetylcholine** receptors, **GABAB** receptors, and most **serotonin** receptors, as well as receptors for **norepinephrine**, **epinephrine**, **histamine**, **dopamine**, **neuropeptides** and **endocannabinoids**.
- Structure - the G protein-coupled receptors have seven hydrophobic transmembrane domains. The protein's N terminus is located on the extracellular side of the membrane and its C terminus is on the intracellular side.
- Metabotropic receptors have neurotransmitters as ligands, which, when bound to the receptors, initiate cascades that can lead to channel-opening or other cellular effects.
- When a ligand, also called the primary messenger, binds to the receptor, or the transducer, the latter activates a primary effector, which can go on to activate secondary messengers .

- Since opening channels by metabotropic receptors involves activating a number of molecules in turn, **channels associated with these receptors take longer to open than ionotropic receptors do**, and they are thus not involved in mechanisms that require quick responses
- Metabotropic receptors also remain open from seconds to minutes.
- They have a much longer-lasting effect than ionotropic receptors, which open quickly but only remain open for a few milliseconds.
- While ionotropic channels have an effect only in the immediate region of the receptor, the effects of metabotropic receptors can be more widespread through the cell.
- Metabotropic receptors can both open and close channels.
- Metabotropic receptors on the presynaptic membrane can inhibit or, more rarely, facilitate neurotransmitter release from the presynaptic neuron

The classical neurotransmitters

- Amines
  - Monoamines
    - catecholamines (dopamine, noradrenaline, adrenaline)
    - indoleamines (serotonin, melatonin)
  - Quaternary amines
    - acetylcholine
- Amino acids (glutamate, GABA, aspartate, glycine)

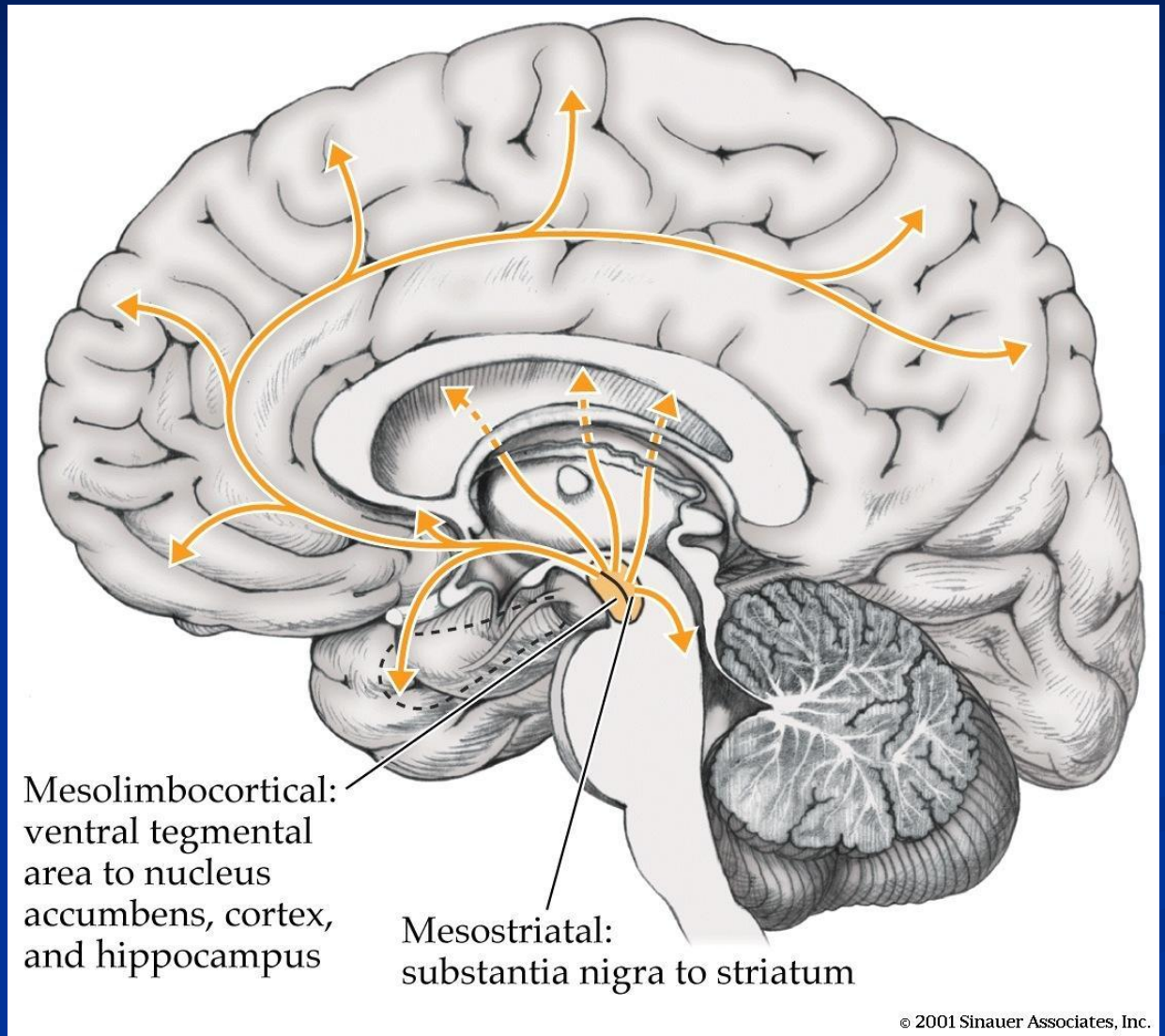
Catecholamine synthesis



-this is *not* for torture
-understanding synthesis can be important for understanding drug action

Catecholamines

Dopamine

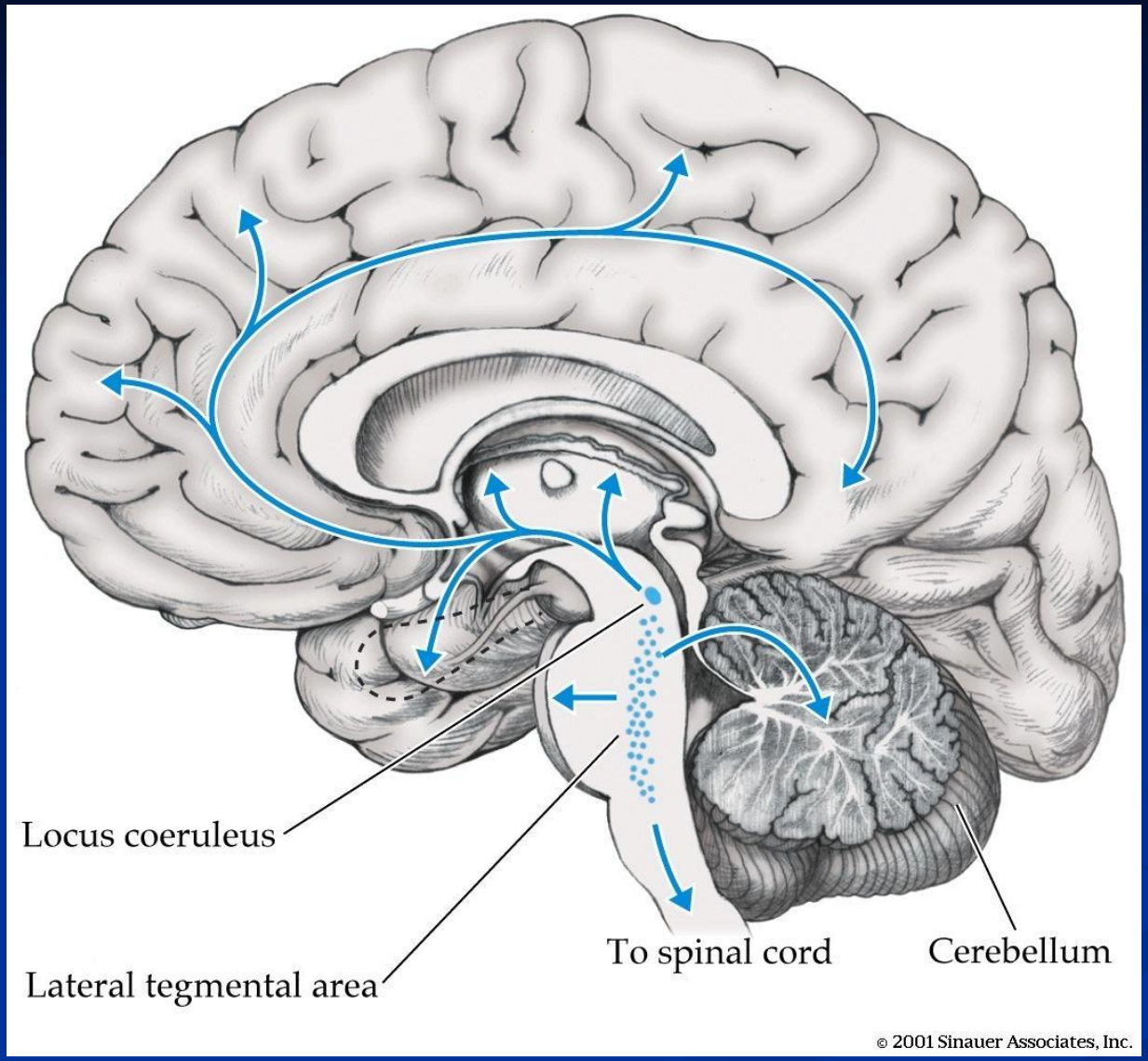


Subtantia nigra and Parkinson's disease

Mesocorticolimbic system and schizophrenia

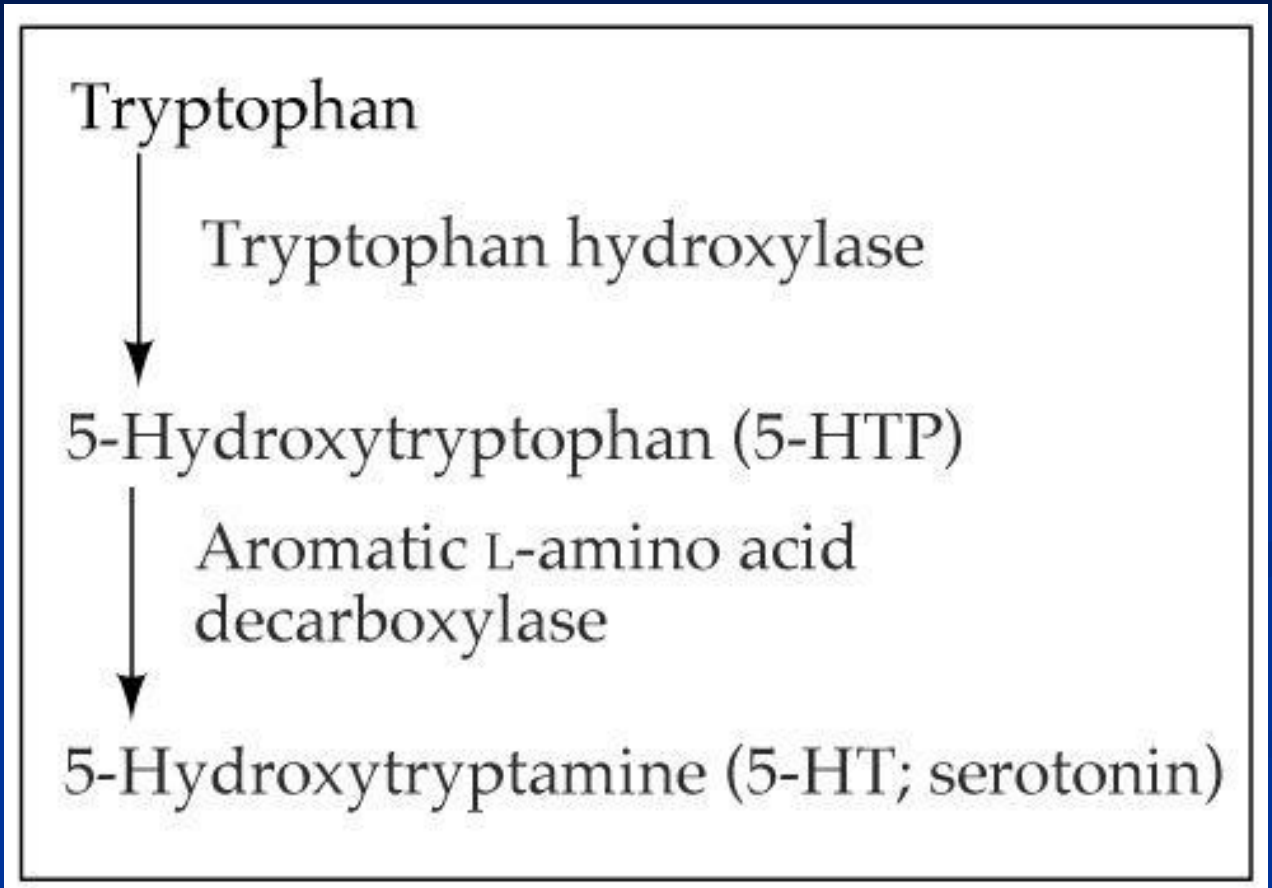
Receptor specificity

Catecholamines



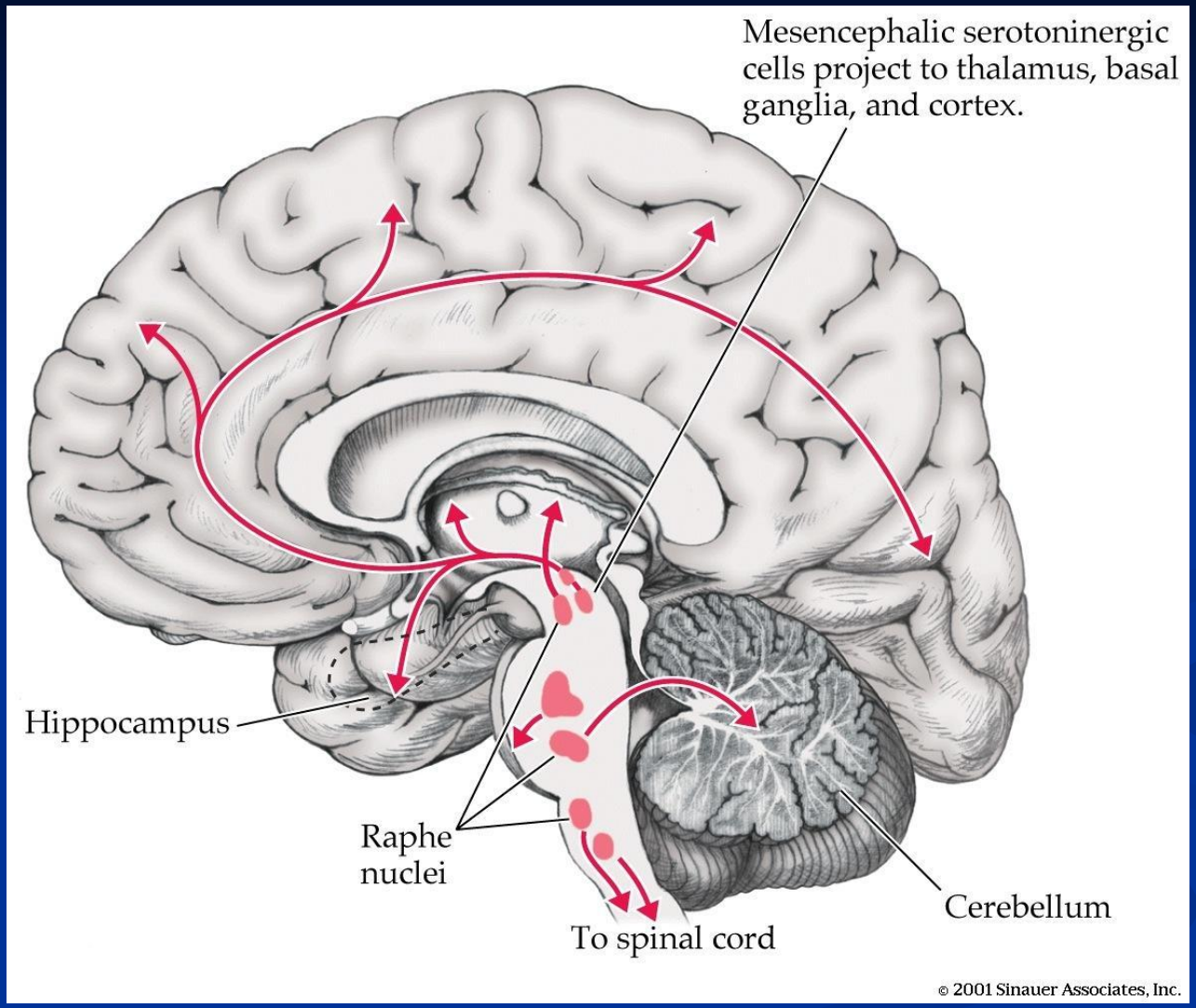
Noradrenergic pathways in the brain
-locus coeruleus

Serotonin synthesis



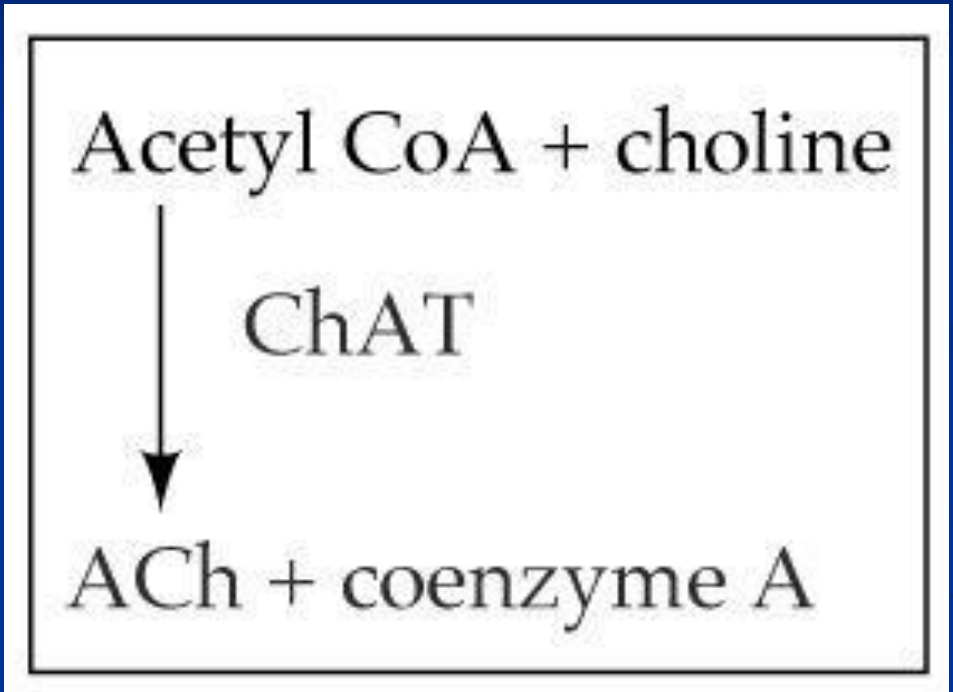
5 HT – Serotonin – 5-hydroxytryptamine

Serotonin

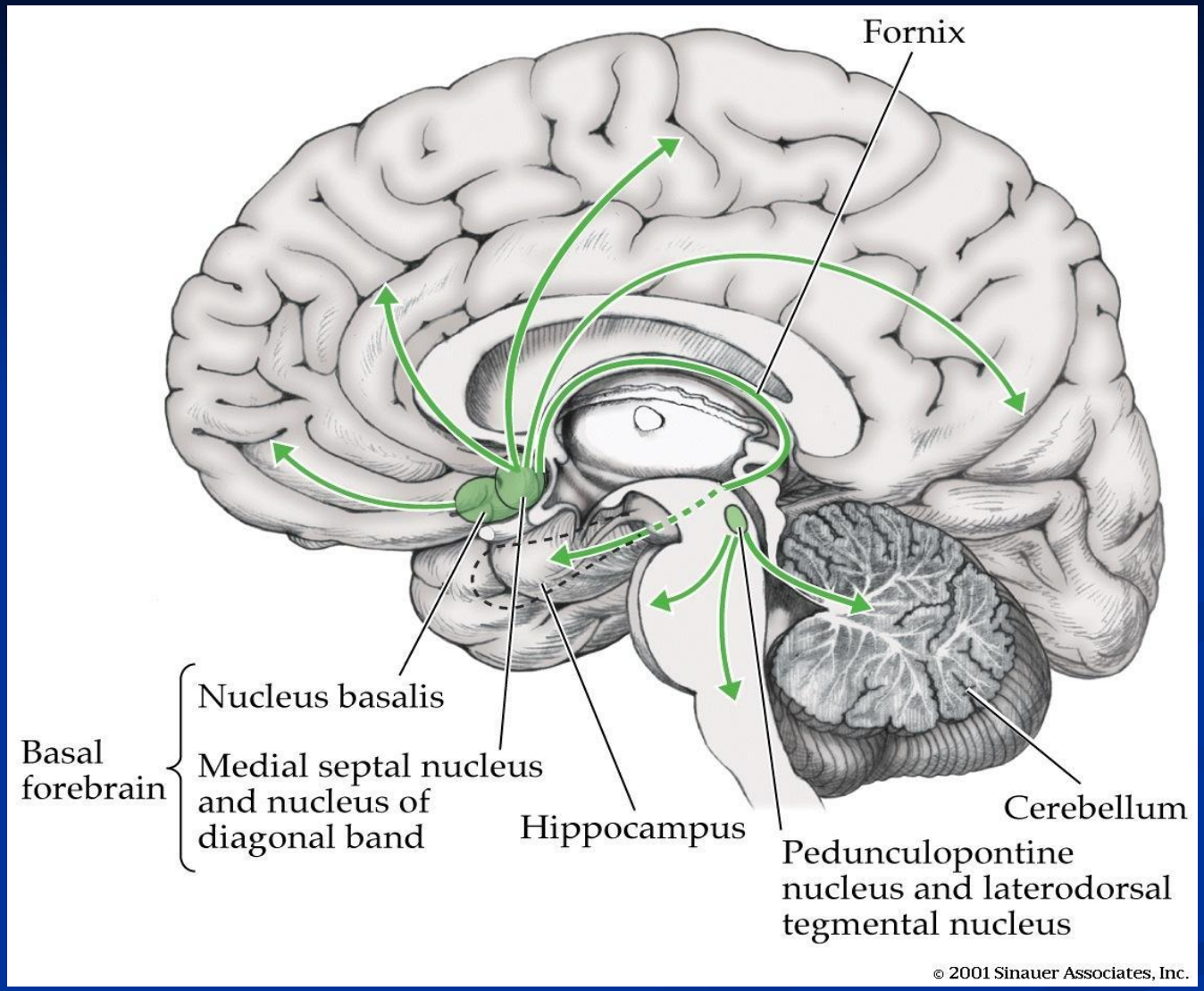


Serotonergic pathways in the brain
-raphe, 16 subtypes

Acetylcholine synthesis



Acetylcholine



Amino acids: The workhorses of the neurotransmitter family

Glutamate - the primary excitatory neurotransmitter in brains

GABA (Gamma-amino-butyric-acid) - the primary inhibitory neurotransmitter

Amino Acid NTs

Glutamate

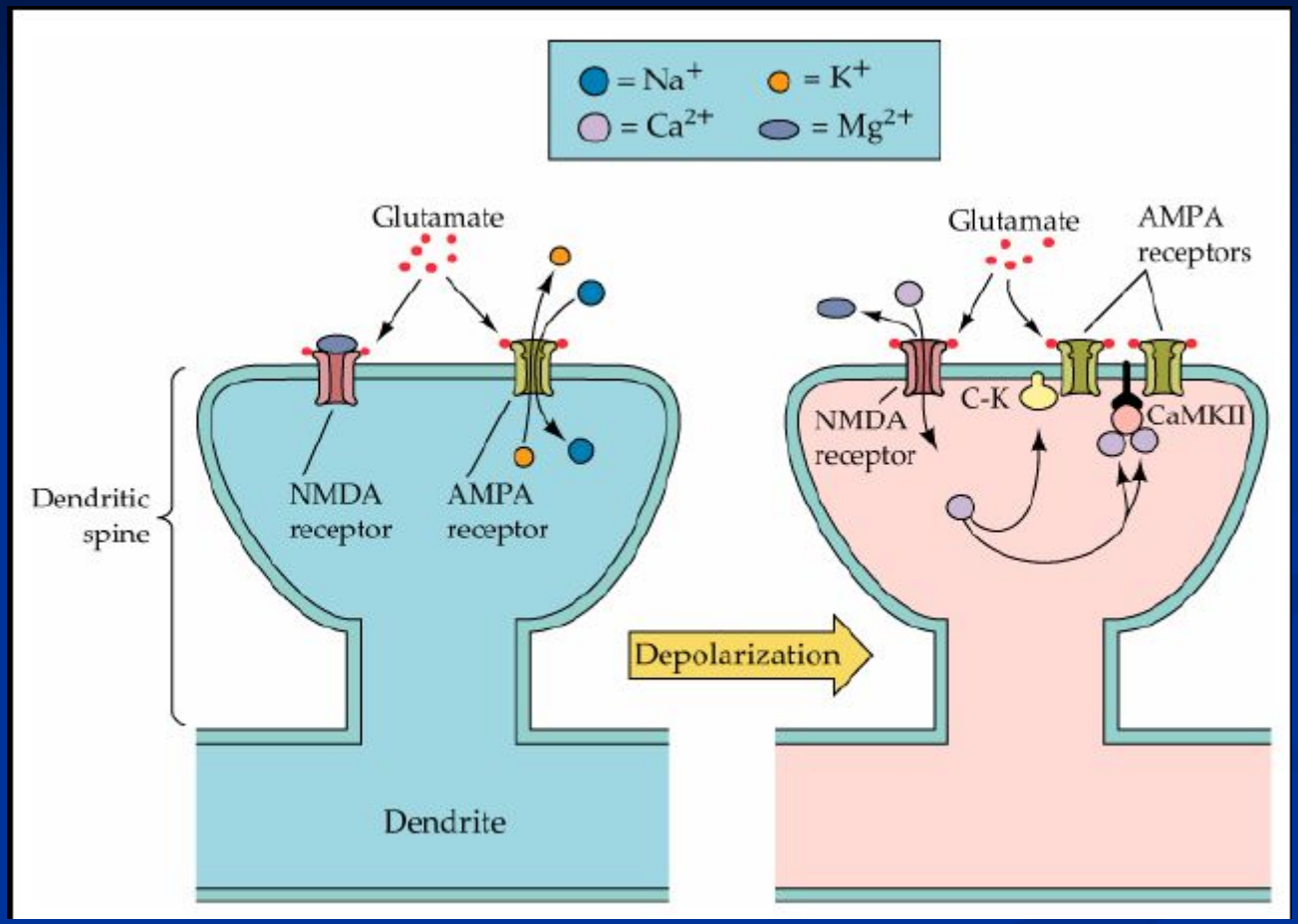
- Uses both ionotropic and metabotropic receptors
- NT of the cerebral cortex
- Excitatory effect

GABA

- Uses ionotropic receptors
- Most prevalent NT in the CNS
- Inhibitory effect

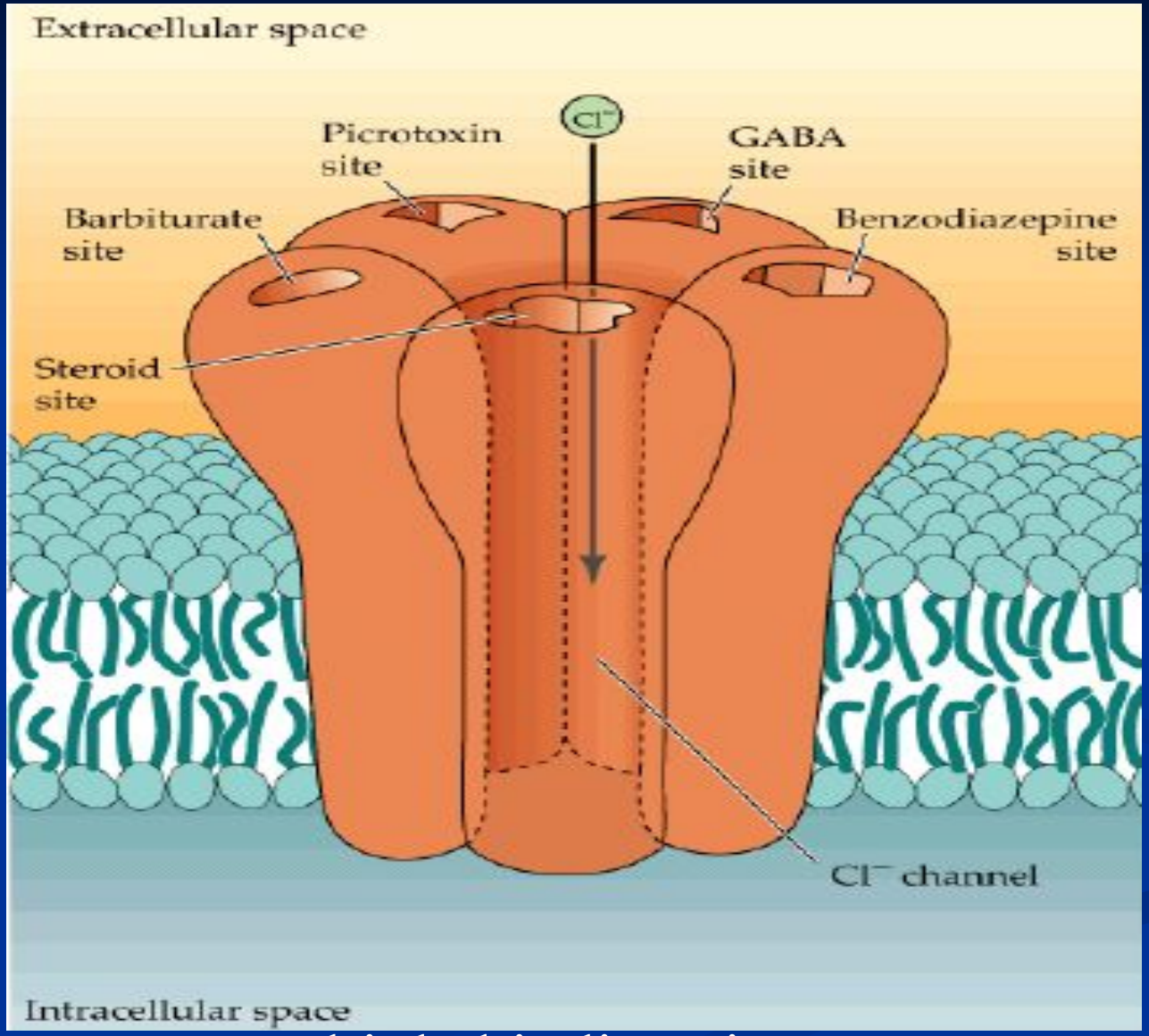
Seizures disorders are the caused by overactive Glu and/or under active GABA

The fabulous glutamate receptor



Activation of NMDA receptor can cause changes in the numbers of AMPA receptors – a mechanism for learning?

The fabulous GABA receptor



Multiple binding sites

Drugs that Block Reuptake

- SSRIs (Serotonin Specific Reuptake Inhibitors)
- Cocaine
- - highly addictive, both physiologically and
- psychologically

Dose-Response Curves

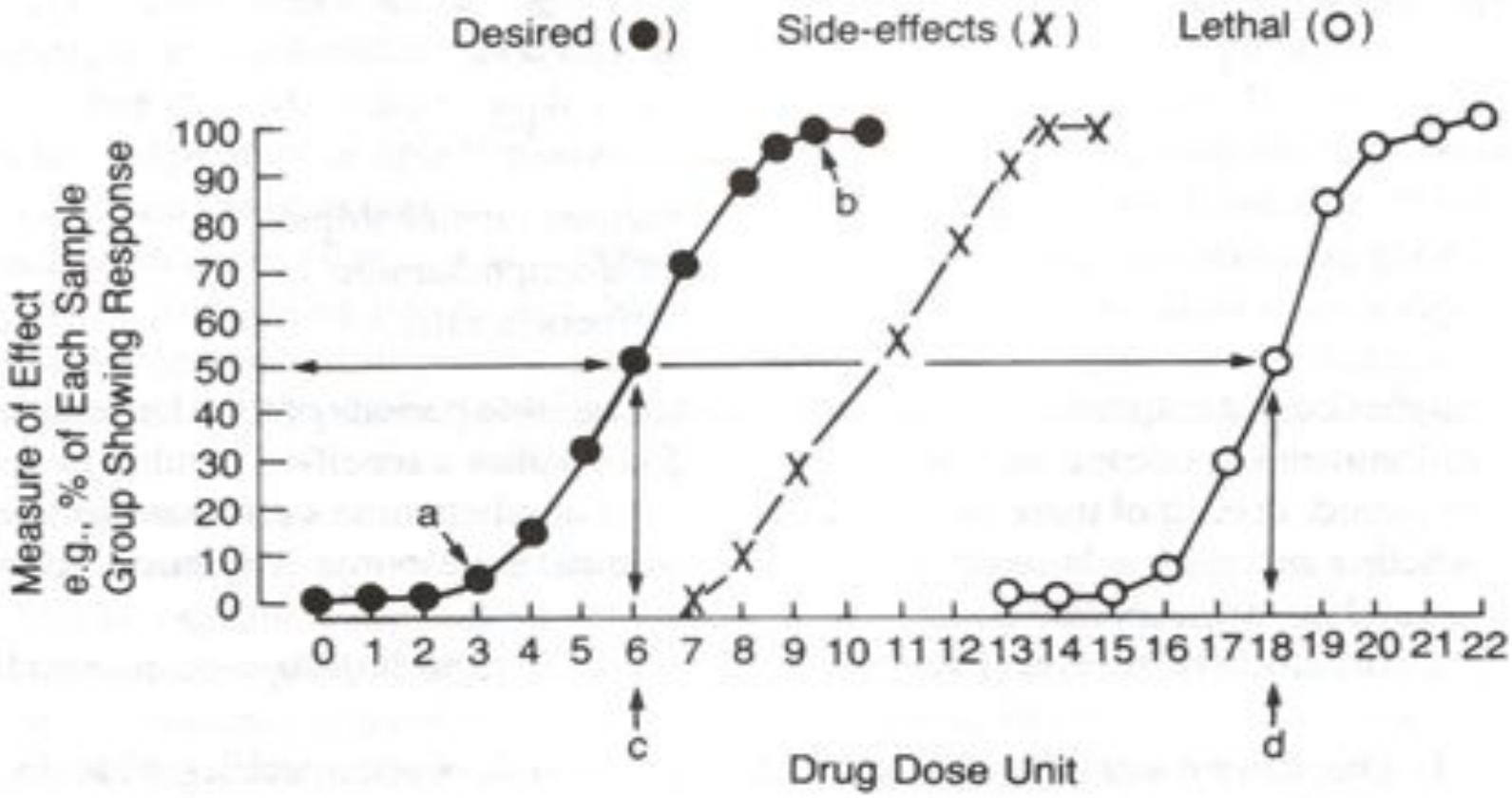
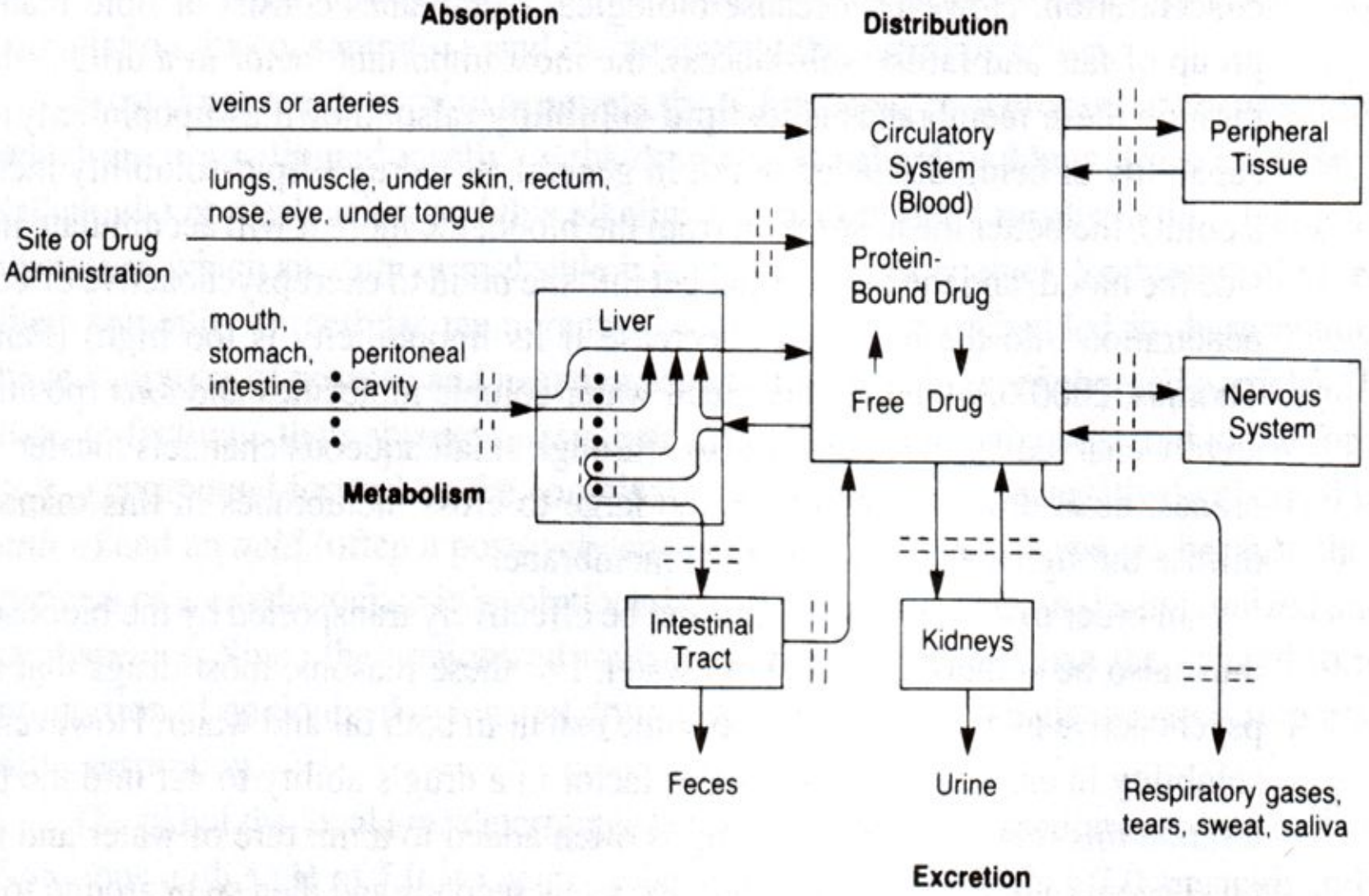


FIGURE 2–2 Stylized dose–response functions depicting (*a*) the threshold dose, (*b*) maximal (desired) response, (*c*) the ED50 of the drug, and (*d*) the LD50 of the drug.

Pharmacokinetics

- Blood Brain Barrier
  - Blocks many chemicals in general circulation from entering the brain
  - The capillaries that supply blood to the brain have tightly packed lipid endothelial cells that block many chemicals
    - Acids
    - Lipid-insoluble chemicals
    - Chemicals bound to plasma proteins
  - Also blocks many hormones from acting centrally
  - Some role may be also be played by astrocytes
    - Astrocytes have processes that contact capillary walls, and others that contact neurons

Pharmacokinetics



Pharmacokinetics

- Liver P450 Enzymes
  - Everything absorbed from the GI tract passes through the liver before entering general circulation
    - Results in *first-pass metabolism*
    - Also metabolizes drugs already in circulation
  - Levels of P450 enzymes can change in response to long-term drug use
    - Can be a factor in the development of *drug tolerance*
  - Important in many drug interactions
    - If two drugs (e.g. barbiturates and ethanol) share a common metabolic pathway, the presence of one will reduce metabolism of the other

Pharmacokinetics

- Liver P450 Enzymes (cont.)
  - Levels of the ~50 P450 enzymes in humans can vary widely between individuals (and ethnicities)
    - In some people one might be missing entirely
    - Important for individual differences in drug reactions
  - Some P450 enzymes actually *activate* drugs
    - Codeine is actually turned into morphine by these enzymes
  - Many drug metabolites are active compounds themselves
    - Can cause side effects, especially 'hangover' effects in long-lasting drugs

Basic classification of drug actions

- Agonists stimulate or activate
- antagonists prevent

Ways that drugs can agonize

- Stimulate release
- receptor binding
- inhibition of reuptake
- inhibition of deactivation
- promote synthesis

Ways that drugs can antagonize

- Block release
- receptor blocker
- prevent synthesis

Schizophrenia

Affects about 1/100 people

Begins in 20's

Often triggered by stress, illness, etc. but there's also a genetic predisposition (stress-diathesis theory

Symptoms of schizophrenia

Positive symptoms

-hallucinations, delusions, paranoia

Negative symptoms

-lack of emotion, energy, directedness

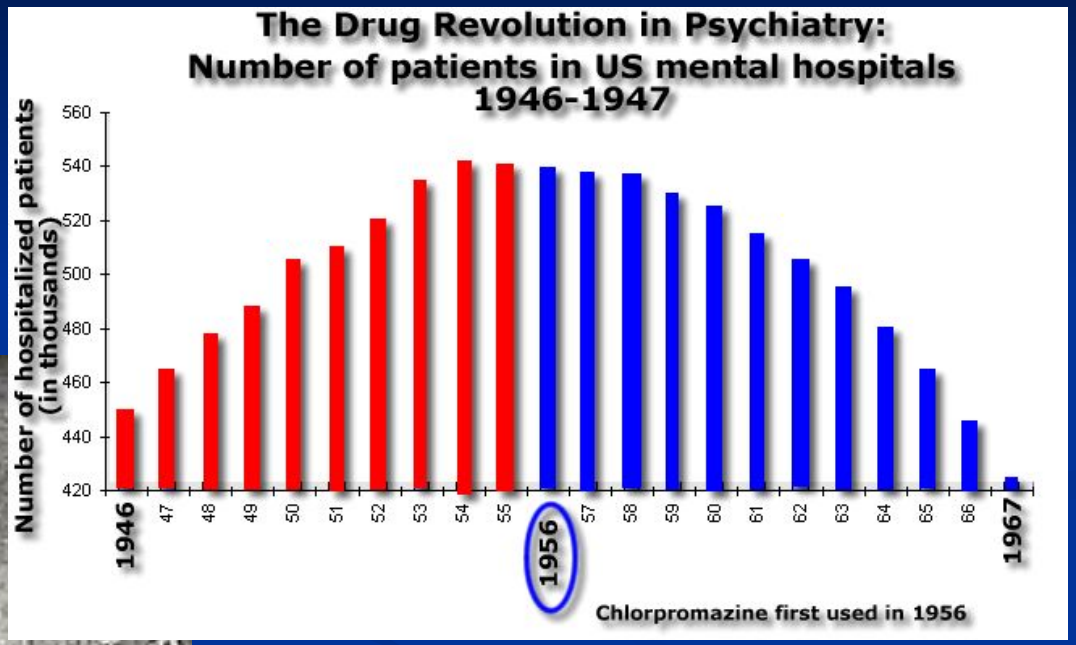
Schizophrenia

- Pathophysiology
  - No consistent neuropathology or biomarkers for schizophrenia
    - ? Increased dopamine in mesolimbic pathways causes delusions and hallucinations
    - ? Dopamine deficiency in mesocortical and nigrostriatal pathways causes negative symptoms (apathy, withdrawal)
    - Hallucinogens produce effect through action on 5-HT2 receptors

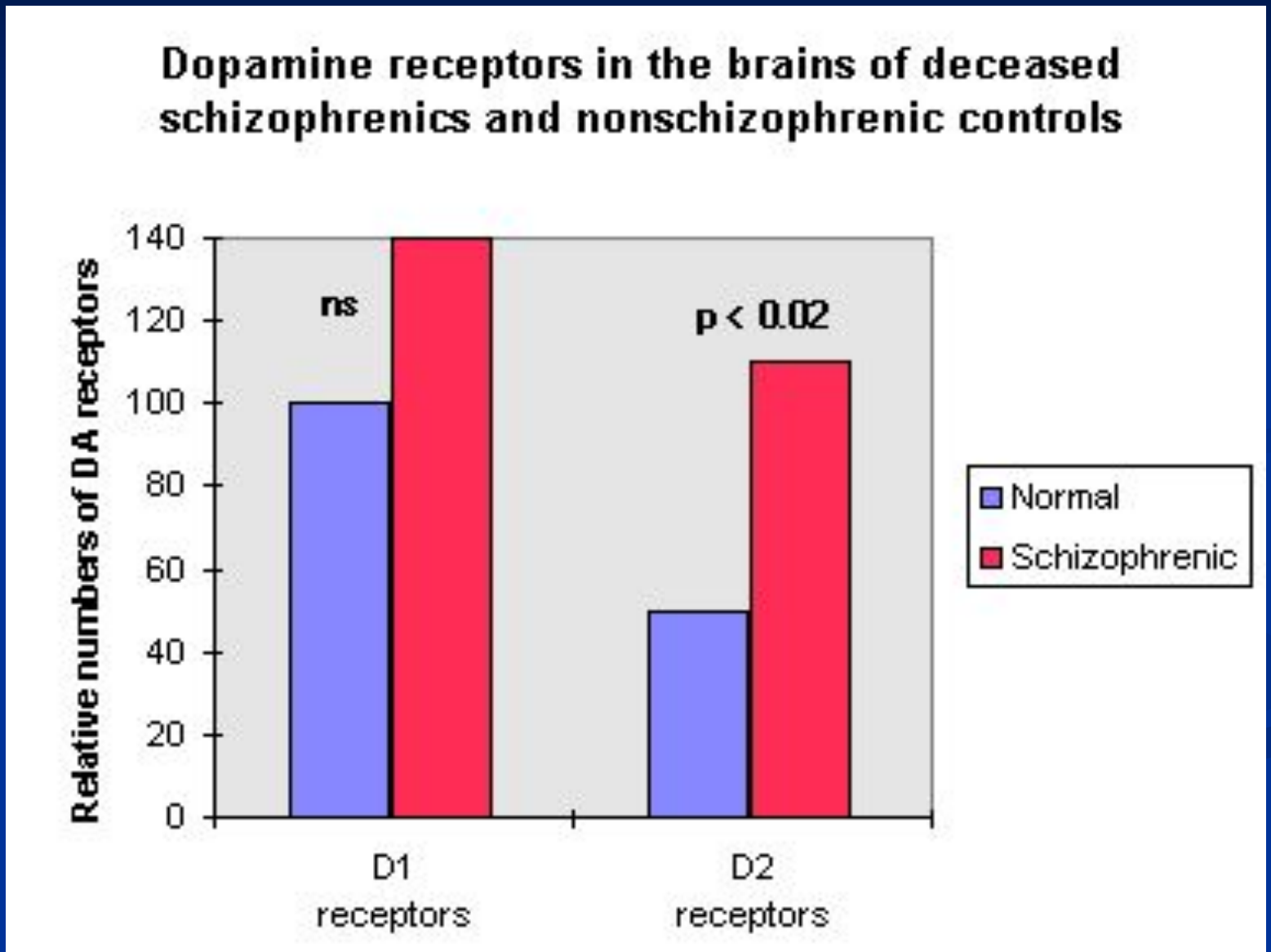
Schizophrenia

- Antipsychotics
  - Typical / Conventional antipsychotics
  - Atypical antipsychotics

The dopamine theory of schizophrenia



Dopamine receptors in normals and schizophrenics



Dopaminergic Neurons

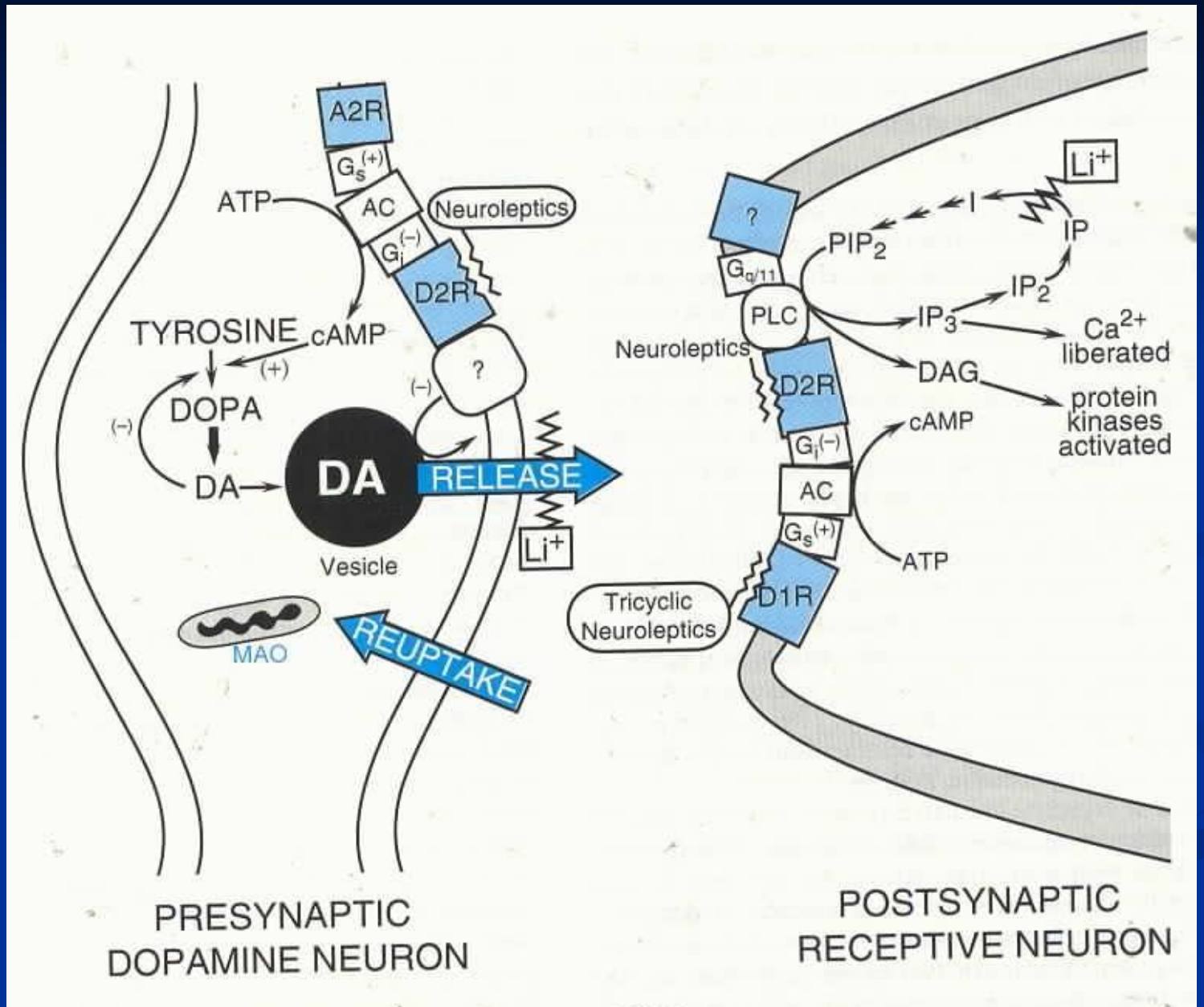


Figure 18–1. Sites of action of neuroleptics and lithium.

Anti-psychotic Drugs

- Antipsychotic drugs (also known as major tranquilizers because they tranquilize and sedate mitigate or eliminate the symptoms of psychotic disorders but they do not cure them.

- Antipsychotic drugs were initially called neuroleptics because they were found to cause neurolepsy, which is an extreme slowness or absence movement

Typical / conventional antipsychotics

Dopamine receptors in various tracks				
Track	Origin	Innervations	Function	Antipsychotic effect
Mesolimbic	Midbrain, Ventral tegmental	Limbic structure, nucleus accumbens	Emotional and intellectual	Hallucinations, deulsions, disordered cognition
Mesocortical	Ventral tegmental	Frontal cortex		
Nigrostriatal	Substantia nigra	Basal ganglia	Extrapyramidal system movement	Motor symptomatology
Tubero-infundubular	Hypothalamus	Pituitary gland	Regulate endocrine functions	Plasma prolactin levels

Typical / conventional antipsychotics

- Mechanism of action
  - Blocks receptors for dopamine, acetylcholine, histamine and norepinephrine
  - Current theory suggests dopamine 2 (D2) receptors suppresses psychotic symptoms
    - All typical antipsychotics block D2 receptors
    - Close correlation between clinical potency and potency as D2 receptor antagonists

Typical / conventional antipsychotics

- Properties
  - Effective in reducing positive symptoms during acute episodes and in preventing their reoccurrence
  - Less effective in treating negative symptoms
    - Some concern that they may exacerbate negative symptoms by causing akinesia
  - Higher incidence of EPS / sedation / anticholinergic adverse effects

Typical / conventional antipsychotics

- Potency
  - All have same ability to relieve symptoms of psychosis
  - Differ from one another in terms of potency
    - i.e. size of dose to achieve a given response
  - When administered in therapeutically equivalent doses, all drugs elicit equivalent antipsychotic response

Typical / conventional antipsychotics

- Low potency
  - Chlorpromazine, thioridazine
- Medium potency
  - Perphenazine
- High potency
  - Trifluoperazine, thiothixene, fluphenazine, haloperidol, pimozide

BRAIN AREAS INVOLVED IN ANTIPSYCHOTIC TREATMENT

- The oversimplified version of what brain areas are involved in anti-psychotic medication use is:
  - Reticular Activating System: the effects on this area generally moderate spontaneous activity and decrease the patients reactivity to stimuli.
  - The Limbic System: the effects on this area generally serves to moderate or blunt emotional arousal.
  - The Hypothalamus: the effects on this areas generally serve to modulate metabolism, alertness, and muscle tone.

- Maisto, S. A., Galizio, M., & Connors, G. J., (2004). Drug Use and Abuse 4th Ed. Wadsworth: USA.

BRAIN AREAS INVOLVED IN SCHIZOPHRENIA
4 DOPAMINE PATHWAYS

- There are four dopamine pathways in the brain:
- Nigrostriatal Dopamine Tract
  - Ascends from the substantia nigra to the neostriatum, which is part of the basal ganglia.
- Mesolimbic Pathway
  - Ascends from the ventral tegmental area (VTA) of the midbrain to the Nucleus Accumbens, septum and amygdala.
- Mesocortical Tract
  - Ascends from the VTA to the prefrontal cortex, cingulate gyrus, and premotor area.
- Hypothalamic-Pituitary Pathway
  - Occur in the hypothalamus and extend to the pituitary gland

1. Heinrichs, R. W., (2001). In Search of Madness: Schizophrenia and Neuroscience. Oxford University Press: New York.

Dopamine Pathways
Nigrostriatal

- Chronic blockade can cause
  - Potentially irreversible movement disorder
    - "Tardive Dyskinesia"

Dopamine Pathways
Mesocortical

- May be associated with both positive and negative symptoms
- Blockade may help reduce negative symptoms of schizophrenia
- May be involved in the cognitive side effects of antipsychotics “mind dulling”

Dopamine Pathways
Tuberoinfundibular

- Blockade produces galactorrhea
- Dopamine = PIF (prolactin inhibiting factor)

Dopamine Pathways
Summary

- Four dopamine pathways
  - Appears that blocking dopamine receptors in only one of them is useful

- Blocking dopamine receptors in the other three may be harmful

Dopaminergic D2 Blockade
Possible Clinical Consequences

- Extrapyramidal movement disorders
- Endocrine changes
- Sexual dysfunction

Histamine H1 Blockade
Possible Clinical Consequences

- Sedation, drowsiness
- Weight gain
- Hypotension

Alpha-1 receptor blockade
Possible clinical consequences

- Postural hypotension
- Reflex tachycardia
- Dizziness

Muscarinic receptor blockade
Possible clinical consequences

- Blurred vision
- Dry mouth
- Sinus tachycardia
- Constipation
- Urinary retention
- Memory dysfunction

Extrapyramidal Symptoms
Dopamine Vs Acetylcholine

- Dopamine and Acetylcholine have a reciprocal relationship in the Nigrostriatal pathway.
- A delicate balance allows for normal movement.

Extrapyramidal Symptoms
Dopamine Vs Acetylcholine

- Dopamine blockade:
- A relative increase in cholinergic activity
  - causing EPS
  - Those antipsychotics that have significant anti-ACH activity are therefore less likely to cause EPS

Extrapyramidal Symptoms
Dopamine Vs Acetylcholine

- When high potency antipsychotics are chosen, we often prescribe anti-ACH medication like
  - Cogentin, diphenhydramine, or Artane

Neurological Side Effects:

- Dystonic Reactions:
  - Uncoordinated spastic movements of muscle groups
    - Trunk, tongue, face
- Akinesia:
  - Decreased muscular movements
- Rigidity:
  - Coarse muscular movement
  - Loss of facial expression

Neurological Side Effects:

- Tremors:
  - Fine movement (shaking) of the extremities
- Akathisia:
  - Restlessness
  - Pacing
    - May result in insomnia
- Tardive Dyskinesia:
  - Buccolinguo-masticalory syndrome
  - Choreoathetoid movements

Typical / conventional antipsychotics

Adverse effects

- Extrapyramidal symptoms (EPS)
  - Early reactions – can be managed with drugs
    - Acute dystonia
    - Parkinsonism
    - Akathisia
  - Late reaction – drug treatment unsatisfactory
    - Tardive dyskinesia (TD)
  - Early reactions occur less frequently with low potency drugs
  - Risk of TD is equal with all agents

Typical / conventional antipsychotics

Adverse effects

- Parkinsonism (neuroleptic induced)
  - Occurs within **first month** of therapy
  - Bradykinesia, mask-like facies, drooling, tremor, rigidity, shuffling gait, cogwheeling, stooped posture
  - Shares same symptoms with Parkinson's disease
  - Management
    - Centrally acting anticholinergics (scheduled benztropine / diphenhydramine / benzhexol with antipsychotics) and amantadine
    - Avoid levodopa as it may counteract antipsychotic effects
    - Switch to atypical antipsychotics for severe symptoms

Typical / conventional antipsychotics

Adverse effects

- Akathisia
  - Develop within **first 2 months** of therapy
  - Compulsive, restless movement
  - Symptoms of anxiety, agitation
  - Management
    - Beta blockers (propranolol)
    - Benzodiazepines (e.g. lorazepam)
    - Anticholinergics (e.g. benztropine, benzhexol)
    - Reduce antipsychotic dosage or switch to low potency agent

Tardive Dyskinesia

- Associated with long-term use of antipsychotics
  - (chronic dopamine blockade)
- Potentially irreversible involuntary movements around the buccal-lingual-oral area

Tardive dyskinesia

- Can be precipitated by antipsychotic cessation
- Rate increased with comorbid substance use
- Aetiological hypotheses:
  - Dopamine supersensitivity
  - GABA insufficiency
  - Neurodegenerative hypothesis

Tardive Dyskinesia

- Attempt of decrease dose
  - will initially exacerbate the movements
- Increasing the dose will initially decrease the movements

Typical / conventional antipsychotics

Adverse effects

- Tardive dyskinesia (TD)
  - Develops **months to years** after therapy
  - Involuntary choreoathetoid (twisting, writing, worm-like) movements of tongue and face
  - Can interfere with chewing, swallowing and speaking
  - Symptoms are usually irreversible

Typical / conventional antipsychotics

Adverse effects

- Tardive dyskinesia (TD)
  - Management
    - Some manufacturers suggest drug withdrawal at earliest signs of TD (fine vermicular movements of tongue) may halt its full development
    - Gradual drug withdrawal (to avoid dyskinesia)
    - Use lowest effective dose
    - Atypical antypsychotic for mild TD
    - Clozapine for severe, distressing TD
    - Inconsistent results with
      - Diazepam, clonazepam, valproate
      - Propranolol, clonidine
      - Vitamin E

Neurological Effects

	Neurological Effects	Tardive Dyskinesia
Onset	Acute or insidious Within 1 – 30 days	After months or years of treatment, especially if drug dose decreased or discontinued
Proposed Mechanism	Due to decreased dopamine	Supersensitivity of postsynaptic dopamine receptors induced by long term neuroleptic blockade
Treatment	Respond to antiparkinsonian drugs	Generally worsen Tardive Dyskinesia Other treatments unsatisfactory; some aimed at balancing Dopaminergic and Cholinergic systems. Can mask symptoms by further suppressing dopamine with neuroleptics. Pimozide or loxapine may least aggravate Tardive Dyskinesia.

Extrapyramidal Effects

Type	Onset	Risk Group	Clinical Course	Treatment
Dystonias	**Acute (within 5 days)**	Young male	Acute, painful, spasmodic Oculogyria may be recurrent	I.M. benztropine, I.M. diphenhydramine, sublingual lorazepam If symptoms recur, oral antiparkinsonian agents can be used
Akathisia	**Insidious to acute (within 10 days)**	12-45% on neuroleptics	May continue though out treatment	I.M. benztropine, I.M. diphenhydramine, sublingual lorazepam If symptoms recur, oral antiparkinsonian agents can be used
Pseudoparkinsonism	Insidious to acute (within 30 days)	12-45% on neuroleptics	May continue through treatment	Oral antiparkinsonian drug. Reduce or change neuroleptic