جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

ماجستير أدوية

أ د حسام الدين النجار

First Term \ 2024-2025

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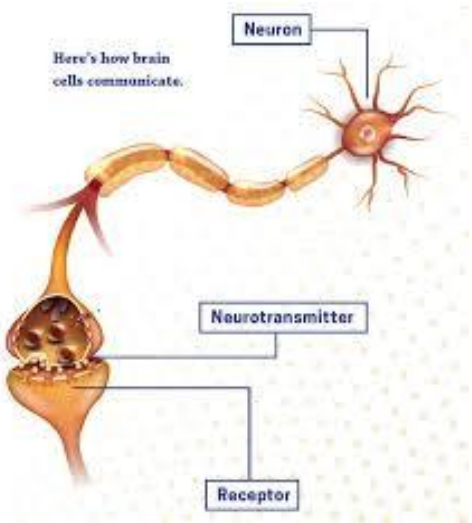
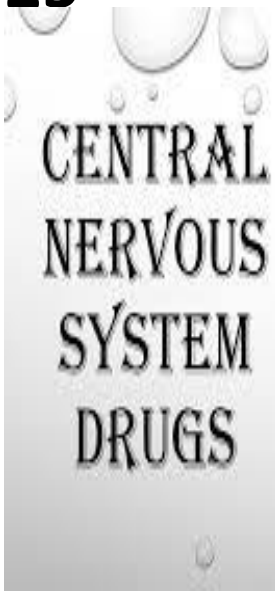
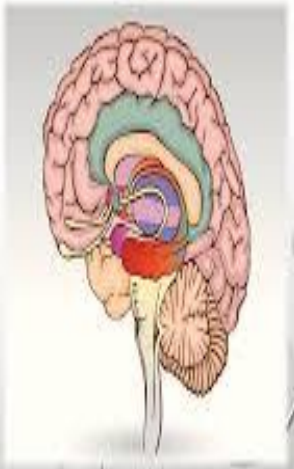


Advanced Pharmacology

CNS DRUGS





CNS DRUGS CLASSIFICATION

- Chemical structure
  - Benzodiazepines, Butyrophenones
- Pharmacological
  - MAO inhibitors, SSRI,
- Clinical use
  - Antidepressants, Antipsychotic agents

Drugs acting on the central nervous system are used more than any other type of agent.

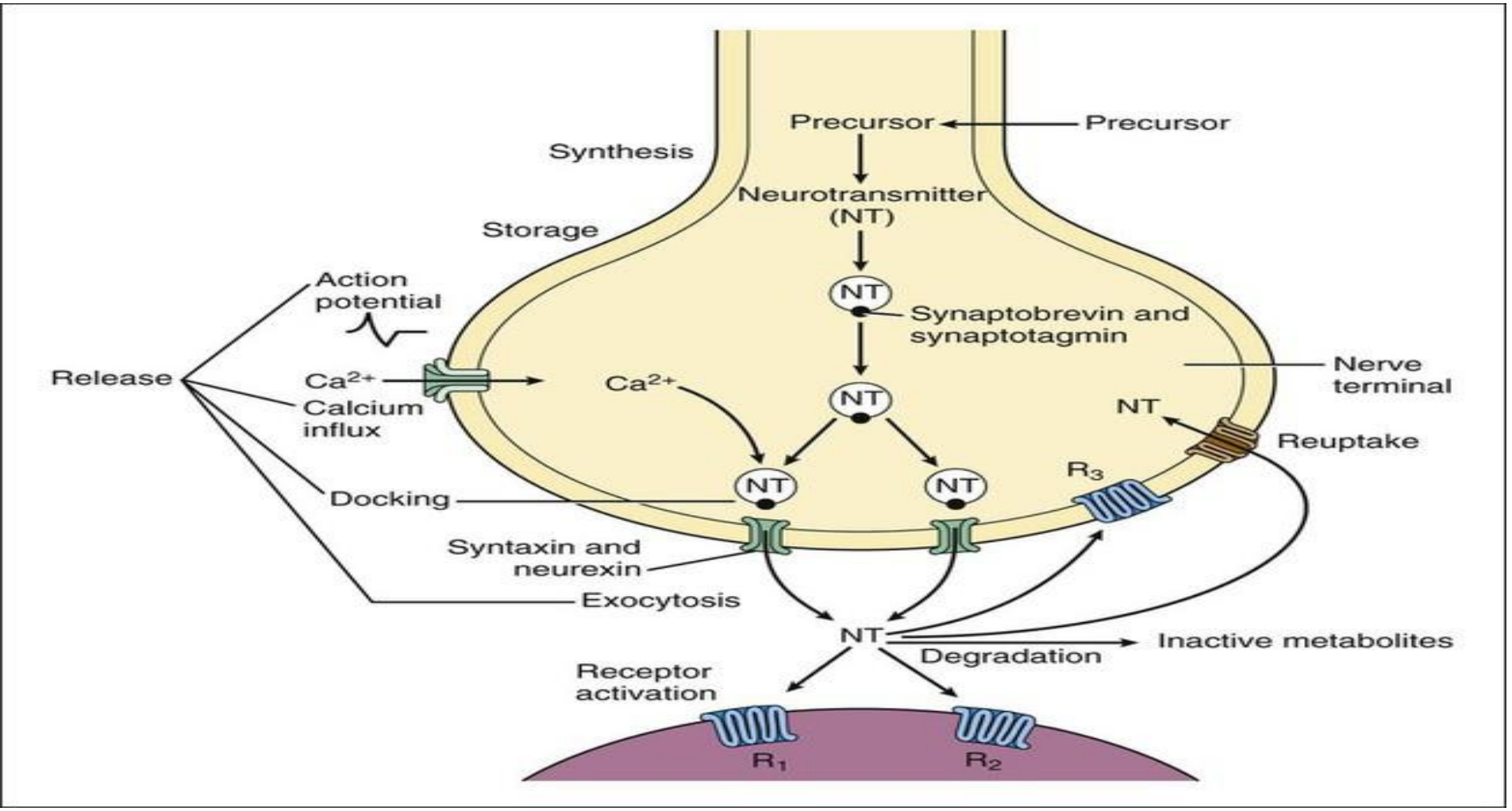
In addition to their therapeutic uses, drugs such as caffeine, alcohol and nicotine are used socially to provide a sense of well-being.

Central drugs often produce dependence with continued use and many are subject to strict legal controls.

The mechanisms by which central drugs produce their therapeutic effects are complex .

Knowledge of central transmitter substances is important because virtually all drugs acting on the brain produce their effects by modifying synaptic transmission.

Central nervous system (CNS) neurotransmission and sites of drug action. **CNS drugs act primarily by affecting the synthesis, storage, release, reuptake, or degradation of neurotransmitters (NT) or by activating receptors. NTs are synthesized from precursors accumulated or synthesized in the neurons. The NTs are stored in vesicles whose membranes contain proteins involved in NT release (synaptobrevin and synaptotagmin). The NTs are released when an action potential–mediated calcium influx initiates interaction of synaptobrevin and synaptotagmin with neuronal membrane-docking proteins (syntaxin and neurexin). This leads to docking and exocytosis. Synaptic NTs can activate presynaptic (R3) or postsynaptic receptors (R1, R2). The action of NTs is terminated by reuptake into the presynaptic neuron or by enzymatic degradation.**



The transmitters used in fast point-to-point neural circuits are amino acids except for a few cholinergic synapses with nicotinic receptors.

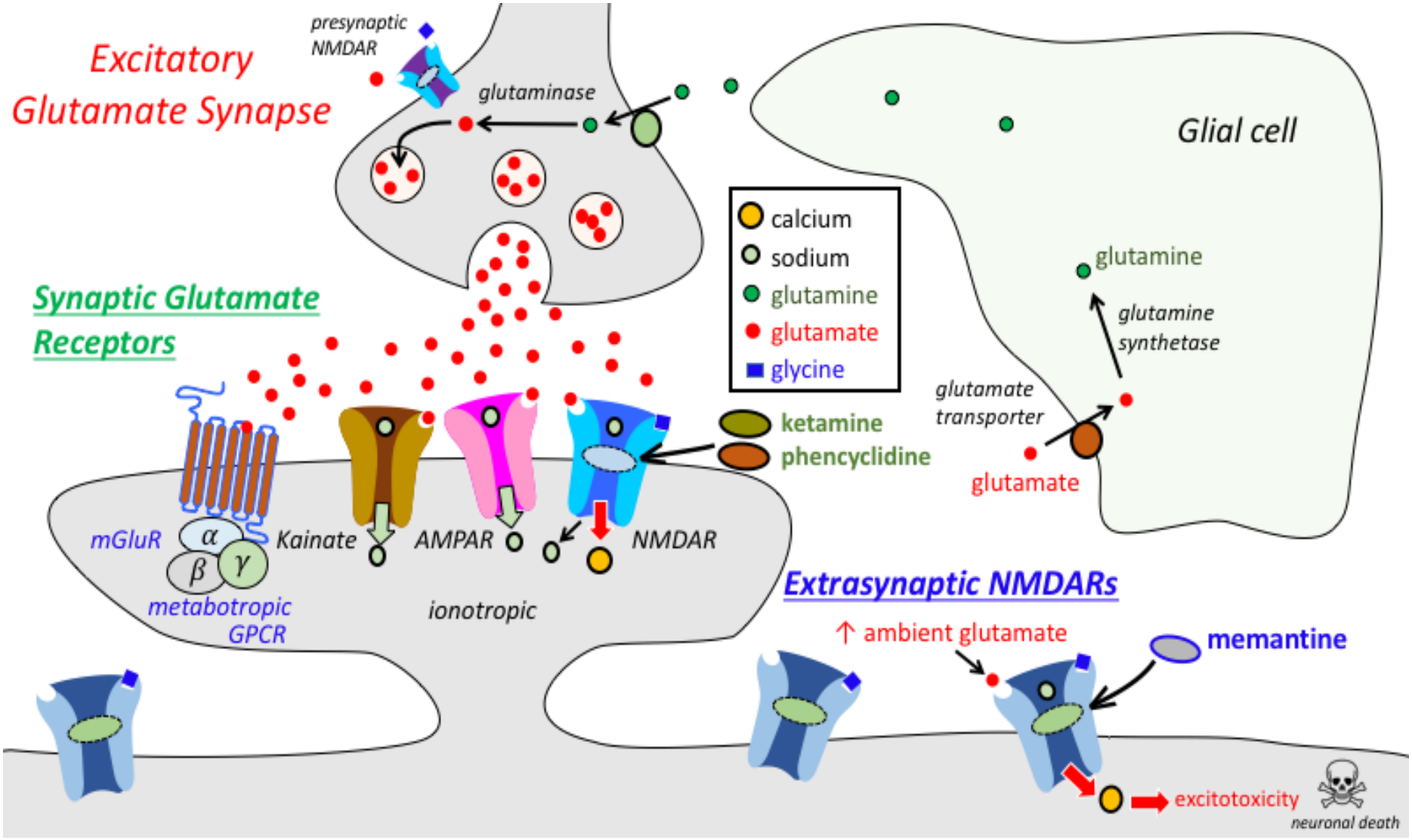
Glutamate is the main central excitatory transmitter. It depolarizes neurones by triggering an increase in membrane Na+ conductance.

γ-Aminobutyric acid (GABA) is the main inhibitory transmitter, perhaps being released at one-third of all central synapses. It hyperpolarizes neurones by increasing their membrane Cl– conductance and stabilizes the resting membrane potential near the Cl– equilibrium potential.

Glycine is also an inhibitory transmitter, mainly in the spinal cord.

AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

NMDAR N-methyl-D-aspartate receptor



Amino acids γ-Aminobutyric acid is present in all areas of the central nervous system, mainly in local inhibitory interneurones.

Drugs that are thought to act by modifying GABAergic synaptic transmission include the benzodiazepines, barbiturates.

Glycine is an inhibitory transmitter in spinal interneurones. It is antagonized by strychnine and its release is prevented by tetanus toxin, both substances causing convulsions.

Glutamate excites virtually all central neurones by activating several types of excitatory amino acid receptor.

GABAA receptors are comprised of five protein subunits surrounding the central chloride ion pore. The most common type of GABA A receptor has two α subunits, two β subunits, and one γ subunit, as seen in the diagram below. The primary binding site, also known as the orthosteric site, is where GABA normally binds to the receptor. The classical GABA A receptor is part of what is called the (GABA A chloride channel receptor complex.)

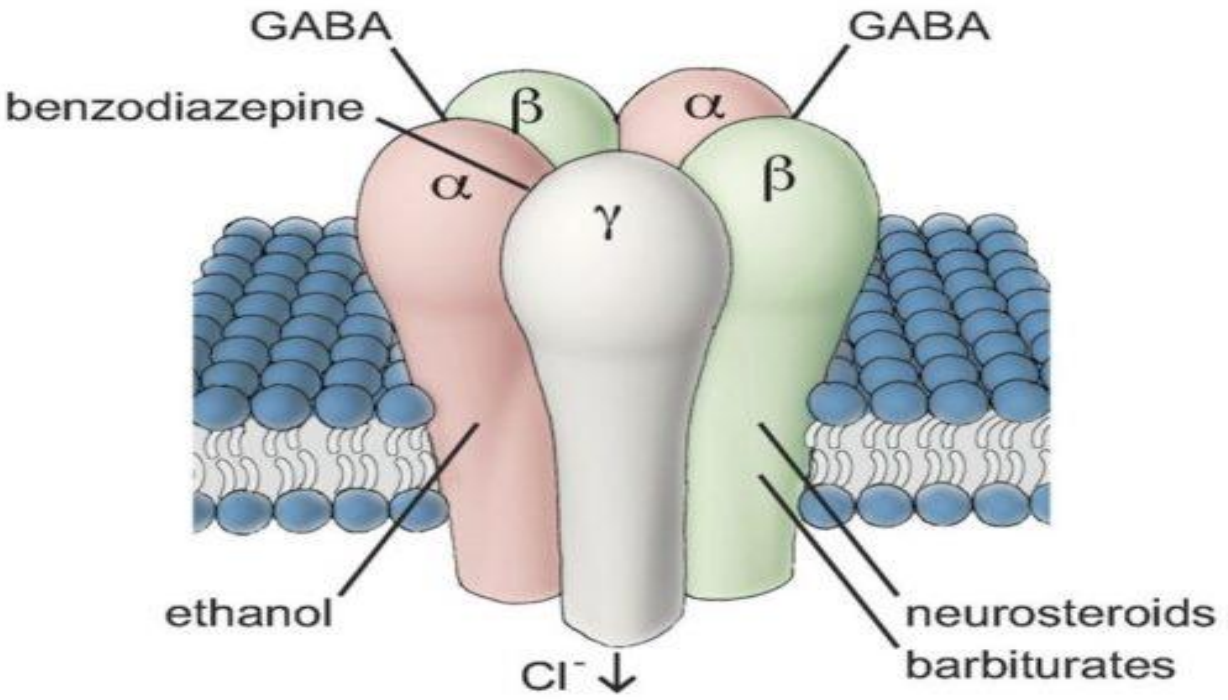


Figure 10.1. The $GABA_A$ Chloride Channel Receptor Complex

Source: https://flipper.diff.org/app/pathways/info/3009

Monoamines Acetylcholine is mainly excitatory in the brain. It is the transmitter released from motorneurone nerve endings at the neuromuscular junction and at collateral axon synapses with Renshaw cells in the spinal cord. The excitatory effects of acetylcholine on central neurones are usually mediated via muscarinic receptors, predominantly of the M1 subtype.

Nicotinic receptors are also present in the brain. They have a different subunit construction (e.g. $\alpha 4\beta 2$) from peripheral receptors and a different pharmacology. Most central nicotinic receptors are presynaptic and increase the release of many other transmitters. However, their only known clinical importance is in nicotine dependence .

Cholinergic neurones are particularly abundant in the basal ganglia and others seem to be involved in cortical arousal responses and in memory. Atropine-like drugs can impair memory and the amnesic action of hyoscine is made use of in anaesthetic premedication .They are also used for their central actions in motion sickness and Parkinson's disease . Loss of cholinergic neurones and memory are prominent features of Alzheimer's disease, for which there is no effective treatment at present. Donepezil, galantamine and rivastigmine are anticholinesterases of modest benefit in up to 50% of patients with Alzheimer's disease.

- **Dopamine generally inhibits central neurones by opening K+ channels. Dopaminergic pathways project from the substantia nigra in the midbrain to the basal ganglia and from the midbrain to the limbic cortex and other limbic structures.**
- **A third (tuberoinfundibular) pathway is involved in regulating prolactin release. The nigrostriatal pathway is concerned with modulating the control of voluntary movement and its degeneration results in Parkinson's disease.**
- **Dopamine agonists are used in the treatment of Parkinson's disease and antagonists (neuroleptics) are used in schizophrenia .**
- **The chemoreceptor trigger zone (CTZ) has dopamine receptors, and dopamine antagonists have antiemetic effects .**

- **Norepinephrine** both inhibits and excites central neurones by activating α2 and α1/β receptors, respectively. **Norepinephrine and dopamine in limbic forebrain structures (especially the nucleus accumbens) are involved in an ascending 'reward' system, which has been implicated in drug dependence .**
- Ascending noradrenergic pathways are also involved in arousal, especially in response to unfamiliar or threatening stimuli.
- Depressed patients are often unresponsive to external stimuli (low arousal) and impairment of noradrenergic function may be associated with depression .
- **Norepinephrine in the medulla is involved in blood pressure regulation .**

- **Serotonin (5-hydroxytryptamine, 5HT) occurs in cell bodies in the raphe nucleus of the brainstem that projects to many forebrain areas and to the ventral and dorsal horns of the spinal cord.**
- The latter descending projection modulates pain inputs . 5HT path ways are involved in feeding behaviour, sleep and mood. 5HT may, like norepinephrine, be involved in depression.
- **5HT3 receptors occur in the CTZ and antagonists have antiemetic effects.**
- 5HT1D receptors occur in cranial blood vessels and the agonist sumatriptan relieves migraine by constricting the vessels that are abnormally dilated during the attack.
- **5HT is involved in the control of sensory transmission and 5HT2 agonists (e.g. LSD) cause hallucinations .**

These neurons project to other parts of the limbic system and the cortex through ascending serotonin pathways. In non-anxious people, these pathways have a normal level of activity. Yet, in people with anxiety disorders, these pathways are overactive.

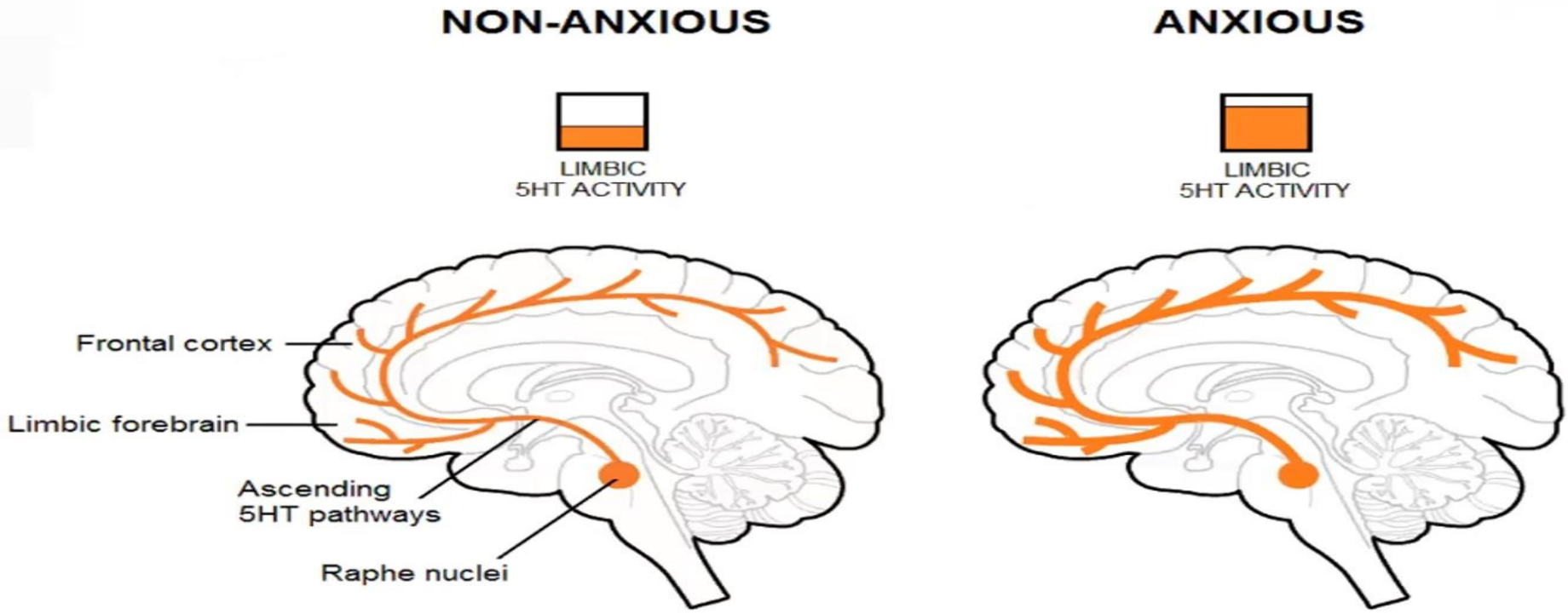
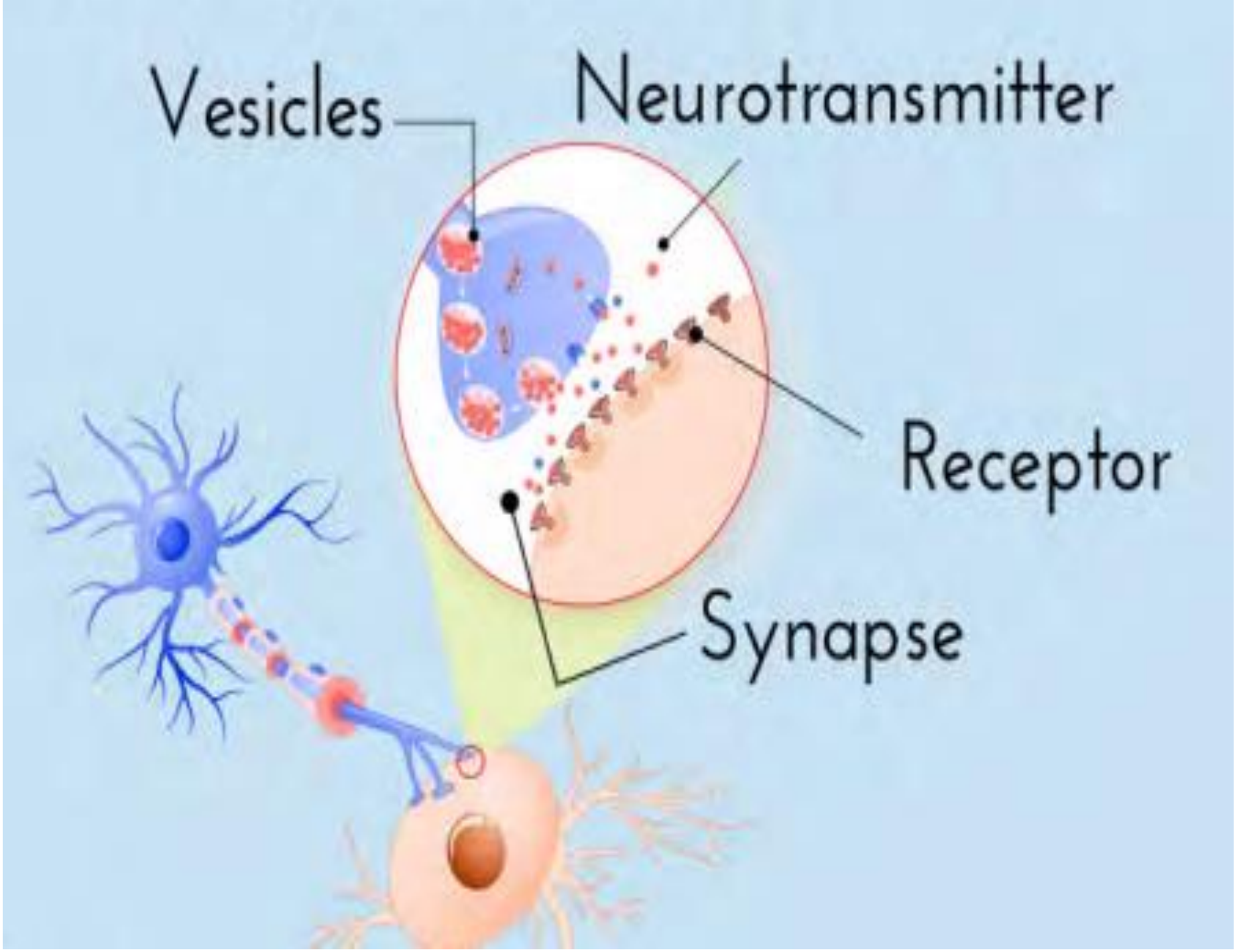
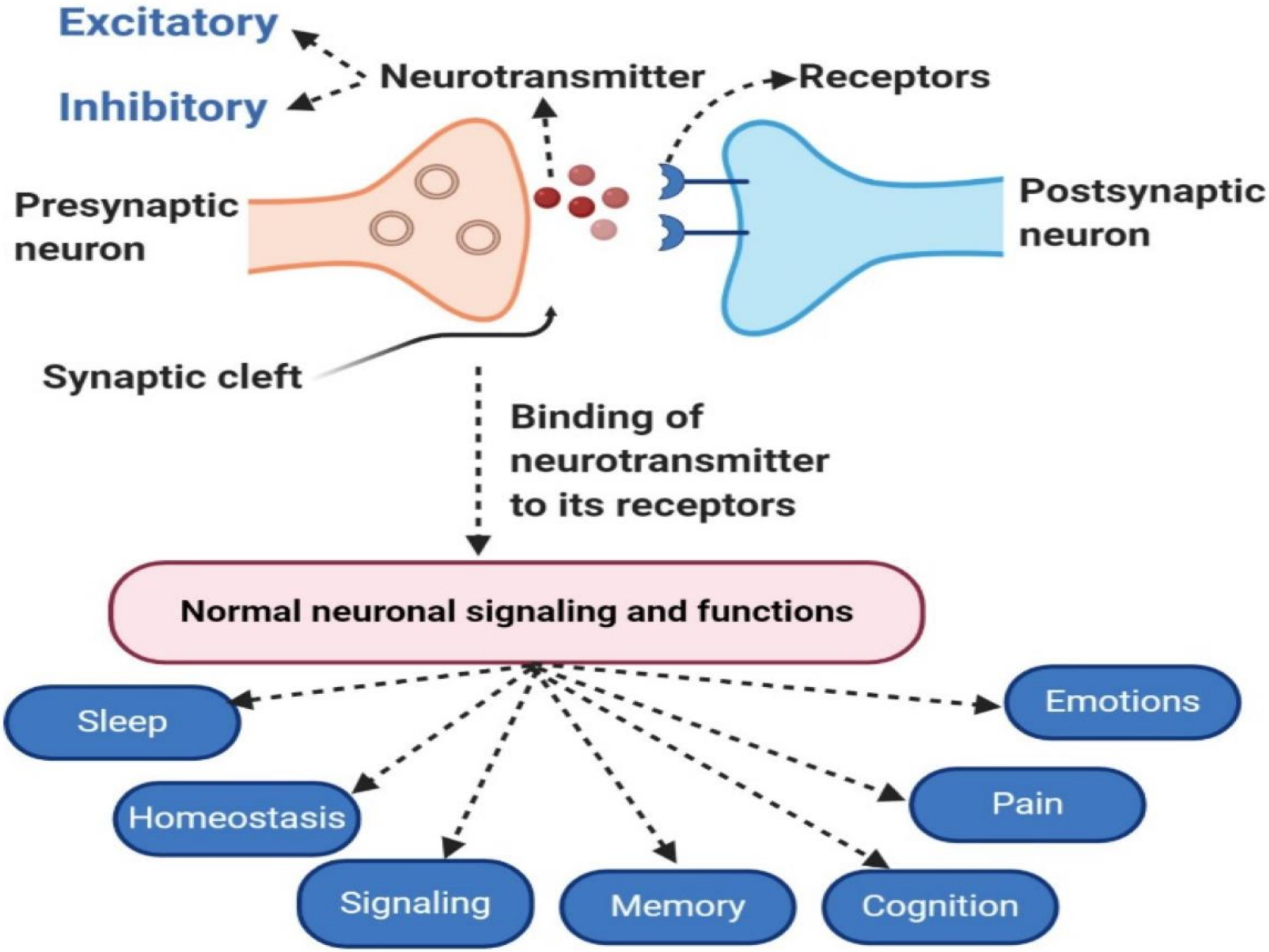


Figure 17.3. Serotonin Hypothesis of Anxiety Disorders

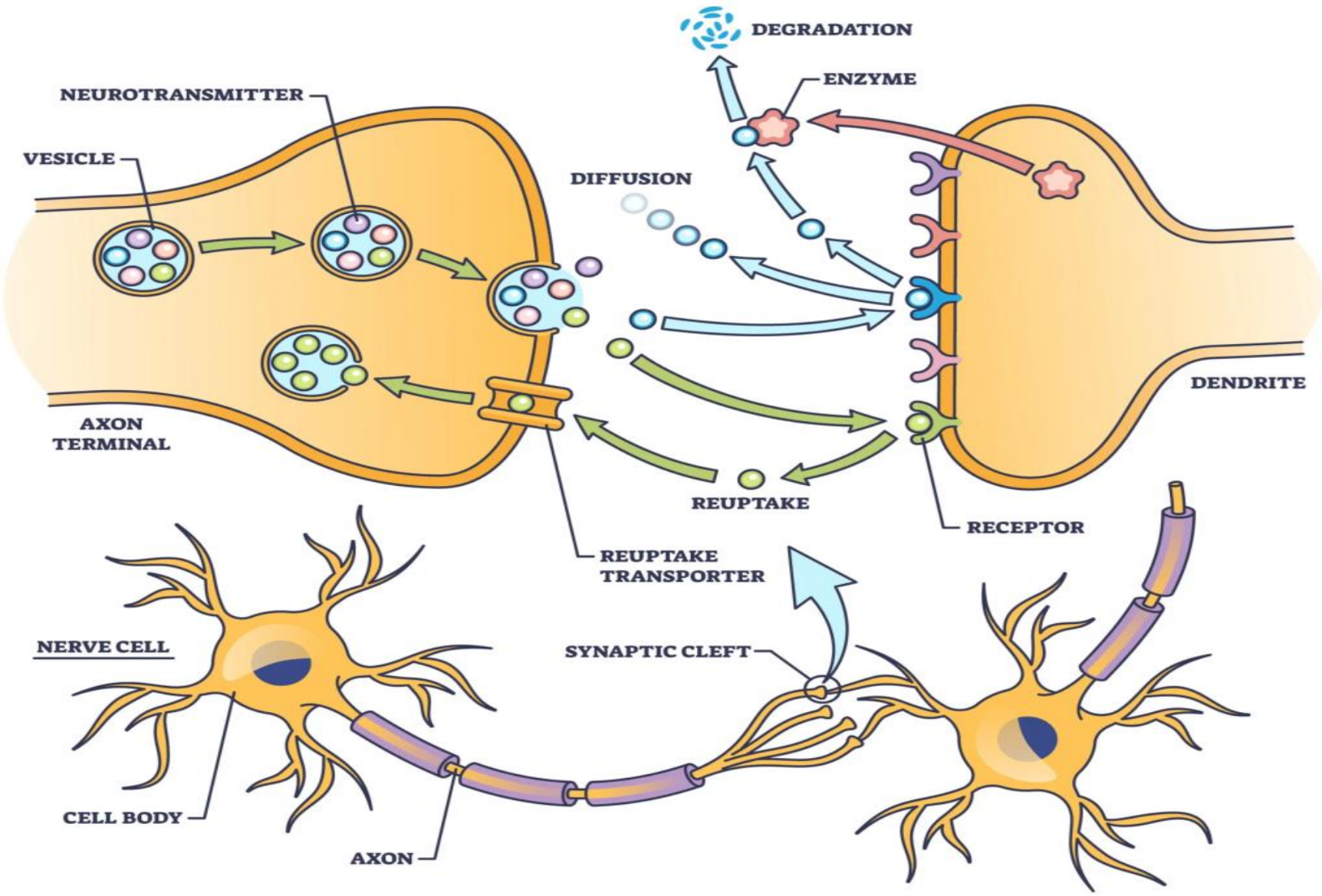
Original drawing by Raymond M. Quock

- **Histamine is a relatively minor transmitter in the brain, but H1 antagonists cause sedation and have antiemetic actions**
- Neuropeptides form the most numerous group of central transmitters. Substance P and the enkephalins are involved in pain path ways Opioids are agonists at enkephalin receptors.
- **Nitric oxide (NO). Nitric oxide synthase (NOS) is present in about 1–2% of neurones in many areas of the brain, e.g. cerebral cortex, hippocampus, striatum.**


Vesicles
Neurotransmitter
Receptor
Synapse


Excitatory
Inhibitory
Neurotransmitter
Receptors
Presynaptic neuron
Postsynaptic neuron
Synaptic cleft
Binding of neurotransmitter to its receptors
Normal neuronal signaling and functions
Sleep
Emotions
Homeostasis
Pain
Signaling
Memory
Cognition

NEUROTRANSMITTER



General Anesthesia

Is the absence of sensation associated with a reversible loss of consciousness. Numerous agents ranging from inert gases to steroids produce anesthesia in animals, but only a few are used clinically .

Anaesthetics depress all excitable tissues, including central neurones, cardiac muscle, and smooth and striatal muscle. However, these tissues have different sensitivities to anaesthetics, and the areas of the brain responsible for consciousness are among the most sensitive.

Thus, it is possible to administer anaesthetic agents at concentrations that produce unconsciousness without unduly depressing the cardiovascular and respiratory centres or the myocardium. However, for most anaesthetics, the margin of safety is small.

General anaesthesia usually involves the administration of different drugs for:

- premedication
- induction of anaesthesia
- maintenance of anaesthesia .

<u>Premedication has two main aims:</u>

1\ the prevention of the parasympathomimetic effects of anaesthesia (bradycardia, bronchial secretion) … (e.g. hyoscine) .

2 \ the reduction of anxiety or pain… SEDATIVE .

Induction is most commonly achieved by the intravenous injection of propofol or thiopental.

Unconsciousness occurs within seconds and is maintained by the administration of an inhalation anaesthetic.

Halothane was the first fluorinated volatile anaesthetic. However, it is associated with a very low incidence of potentially fatal hepatotoxicity and has largely been replaced with newer, less toxic agents, e.g. sevoflurane and isoflurane.

Nitrous oxide at concentrations of up to 70% in oxygen is the most widely used anaesthetic agent. It is used with oxygen as a carrier gas for the volatile agents, or together with opioid analgesics (e.g. fentanyl). Nitrous oxide causes sedation and analgesia, but it is not sufficient alone to maintain anaesthesia.

Mechanism of action of anaesthetics

- It is not known fully how anaesthetics produce their effects. Because anaesthetic potency correlates well with lipid solubility it was thought that anaesthetics might dissolve in the lipid bilayer of the cell membrane and somehow produce anaesthesia by expanding the membrane or increasing its fluidity.
- **It is now believed that anaesthetics bind to a hydrophobic area of a protein (e.g. ion channel, receptor) and inhibit its normal function.**
- **In support of this idea, anaesthetics have been shown to inhibit the function of glutamate receptors and to enhance γ-aminobutyric acid (GABA)ergic transmission.**

Intravenous agents **These are used mainly for the induction of anaesthesia. Some agents, particularly propofol, are used alone (by continuous infusion) for short surgical procedures. Thiopental is an ultrashort-acting depressant of the central nervous system which induces hypnosis and anesthesia, but not analgesia. Thiopental injected intravenously induces anaesthesia in less than 30 s because the very lipid-soluble drug quickly dissolves in the rapidly perfused brain.**

Recovery from a single dose of thiopental is rapid because of redistribution into less-perfused tissues.

The liver subsequently metabolizes thiopental. Doses of thiopental only slightly above the 'sleep dose' depress the myocardium and the respiratory center. Very occasionally anaphylaxis may occur.


THIOWELL 1000
1 Gm
Thiopental Sodium
Injection
THIOWELL 1000
Thiopental Sodium
Injection
THIOWELL 1000


For Single Patient Use Only
PROPOFOL
Injectable Emulsion
1 g/100 mL (10 mg/mL)
PAA124898
100 mL
LOT:PA90067
EXP:01 MAY 2023


KETAMINE HCl
INJECTION, USP
500 mg/10 mL*
(50 mg/mL)

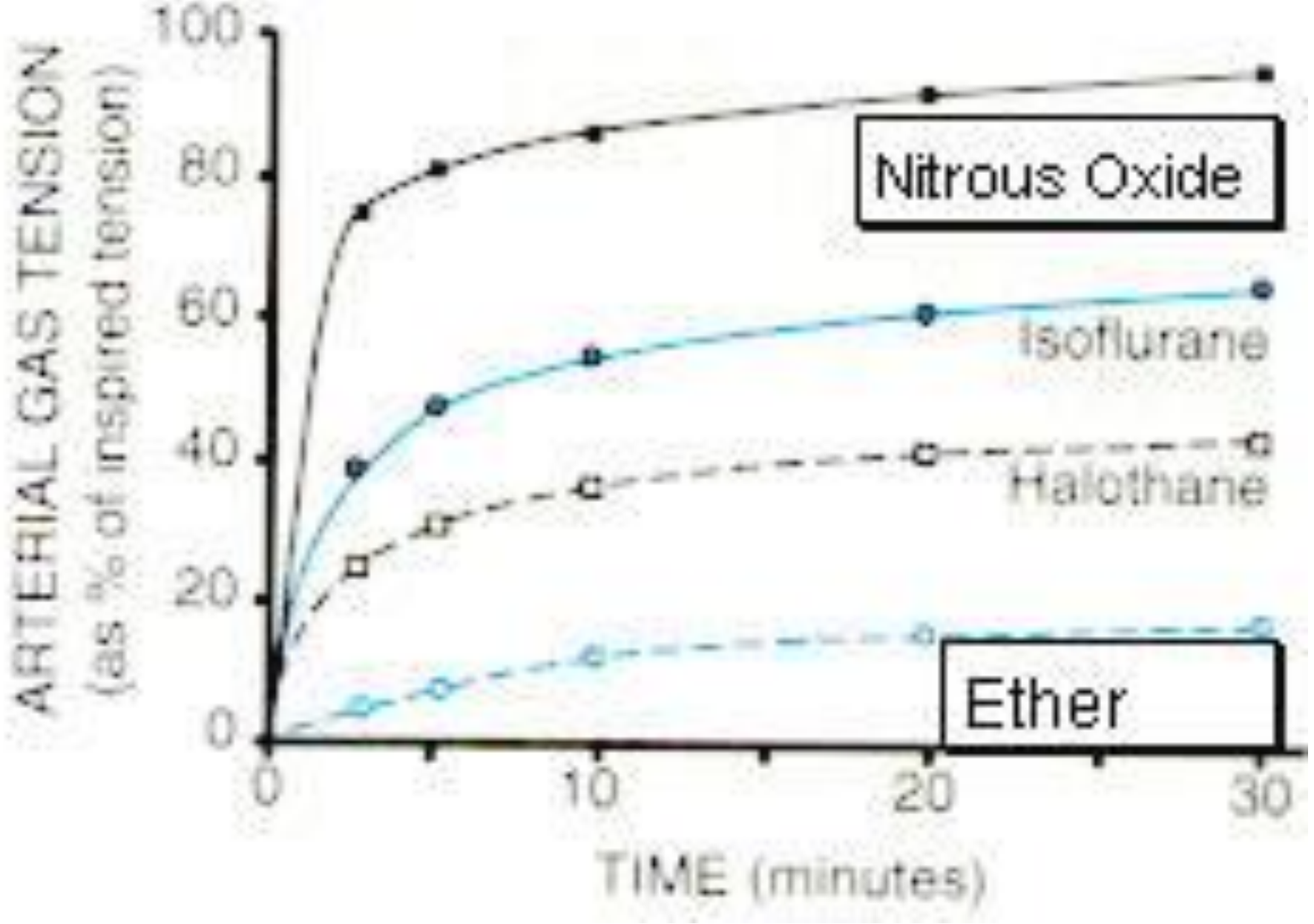

FLUOTHANE
inhalation
anesthetic
250 ml

- Propofol (2,6-diisopropylphenol) induces anaesthesia within 30 s and is smooth and pleasant. **Recovery from propofol is rapid, without nausea or hangover and, for this reason, it has largely replaced thiopental. Propofol is inactivated by redistribution and rapid metabolism, and in contrast to thiopental, recovery from continuous infusion is relatively fast. Ketamine may be given by intramuscular or intravenous injection. It is analgesic in subanaesthetic doses, but often causes hallucinations. Its main use is in paediatric anaesthesia.**

Inhalation agents Uptake and distribution.

The speed at which induction of anaesthesia occurs depends mainly on the solubility of gas in blood and the inspired concentration of gas.

When agents of low solubility (nitrous oxide) diffuse from the lungs into arterial blood, relatively small amounts are required to saturate the blood, and so the arterial tension (and hence brain tension) rises quickly. **More soluble agents (halothane) require the solution of much more anaesthetic before the arterial anaesthetic tension approaches that of the inspired gas**, and so induction is slower. Recovery from anaesthesia is also slower with increasing anaesthetic solubility.


ARTERIAL GAS TENSION
(as % of inspired tension)
100
80
60
40
20
0
0
10
20
30
TIME (minutes)
Nitrous Oxide
Isoflurane
Halothane
Ether

- **Uptake, Distribution, and Elimination**

Unlike more common drug solutions, gases absorb and distribute as the result of pressure gradients and equilibrate when tensions of inspired gas equal those in alveoli, blood, and tissues.

Gases that have low solubility in blood and adipose tissue will achieve tensions and equilibrate more rapidly.

The blood–gas partition coefficient is a ratio of the concentration of volatile anaesthetic in blood compared to alveolar gas once the partial pressure has equilibrated. It is a pharmacological term used to describe the solubility of a volatile anaesthetic agent.

This tension in blood provides the driving force for inhalation agents to enter the brain, where their anesthetic action occurs. nitrous oxide has very low solubility and therefore achieves equilibration most rapidly. For this reason, nitrous oxide has the fastest onset among inhalation agents .

Nitrous oxide is not potent enough to use as a sole anaesthetic agent, but it is commonly used as a non-flammable carrier gas for volatile agents, allowing their concentration to be significantly reduced. It is a good analgesic and a 50% mixture in oxygen (Entonox) is used when analgesia is required (e.g. in childbirth, road traffic accidents). Nitrous oxide has little effect on the cardiovascular or respiratory systems.

Halothane is a potent agent and, as the vapour is non-irritant, induction is smooth and pleasant. It causes a concentration-dependent hypotension, largely by myocardial depression.

Halothane often causes arrhythmias and, because the myocardium is sensitized to catecholamines, infiltration of epinephrine (adrenaline) may cause cardiac arrest. Like most volatile anaesthetics, halothane depresses the respiratory centre.

More than 20% of the administered halothane is biotransformed by the liver to metabolites (e.g. trifluoroacetic acid) that may cause severe hepatotoxicity with a high mortality.

Hepatotoxicity is more likely after repeated exposure to halothane, which should be avoided. Isoflurane has similar actions to halothane but is less cardiodepressant and does not sensitize the heart to epinephrine. It causes dose related hypotension by decreasing systemic vascular resistance.

NURSING PHARMACOLOGY STUDY GUIDES

Anxiolytics & Hypnotics

NERVOUS SYSTEM DRUGS

BENZODIAZEPINES, BARBITURATES

Anxiolytics and hypnotics

Sleep disorders are treated with benzodiazepines (BDZs) or by other drugs that act at the BDZ receptor .

BDZs are now less used in anxiety states .

BDZs have anxiolytic, hypnotic, muscle relaxant, anticonvulsant and amnesic actions, which are thought to be caused mainly by the enhancement of γ-aminobutyric acid (GABA)-mediated inhibition in the central nervous system.

GABA released from nerve terminals binds to GABA A receptors; the activation of these receptors increases the Cl– conductance of the neurone . The GABA A–Cl– channel complex also has a BDZ modulatory receptor site . Occupation of the BDZ sites by BDZ receptor agonists causes a conformational change in the GABA receptor. **This increases the affinity of GABA binding and enhances the actions of GABA on the Cl– conductance of the neuronal membrane .**

The barbiturates act at another binding site and similarly enhance the action of GABA.

- The popularity of BDZs arose from their apparently low toxicity, but it is now realized that chronic BDZ treatment may cause **cognitive impairment, tolerance and dependence.** For these reasons, **BDZs should only be used for 2–4 weeks to treat severe anxiety and insomnia.**

- Many antidepressants are also anxiolytic and because they do not cause sedation and dependence they have become the **first-line drugs in the treatment of chronic anxiety states.**
- **Buspirone is a non sedative anxiolytic that acts at 5-hydroxytryptamine (5HT) synapses. β-Blockers can be useful in anxiety where autonomic symptoms pre dominate (e.g. tremor, tachycardia, sweating).**
- Different BDZs are marketed as hypnotics and anxiolytics . It is mainly the duration of action that determines the choice of drug. Many BDZs are metabolized in the liver to active metabolites, which may have longer elimination half-lives (t1/2) than the parent drug. **For example, diazepam (t1/2 ≈ 20–80 h) has an active N-desmethyl metabolite that has an elimination half-life of up to 200 h.**

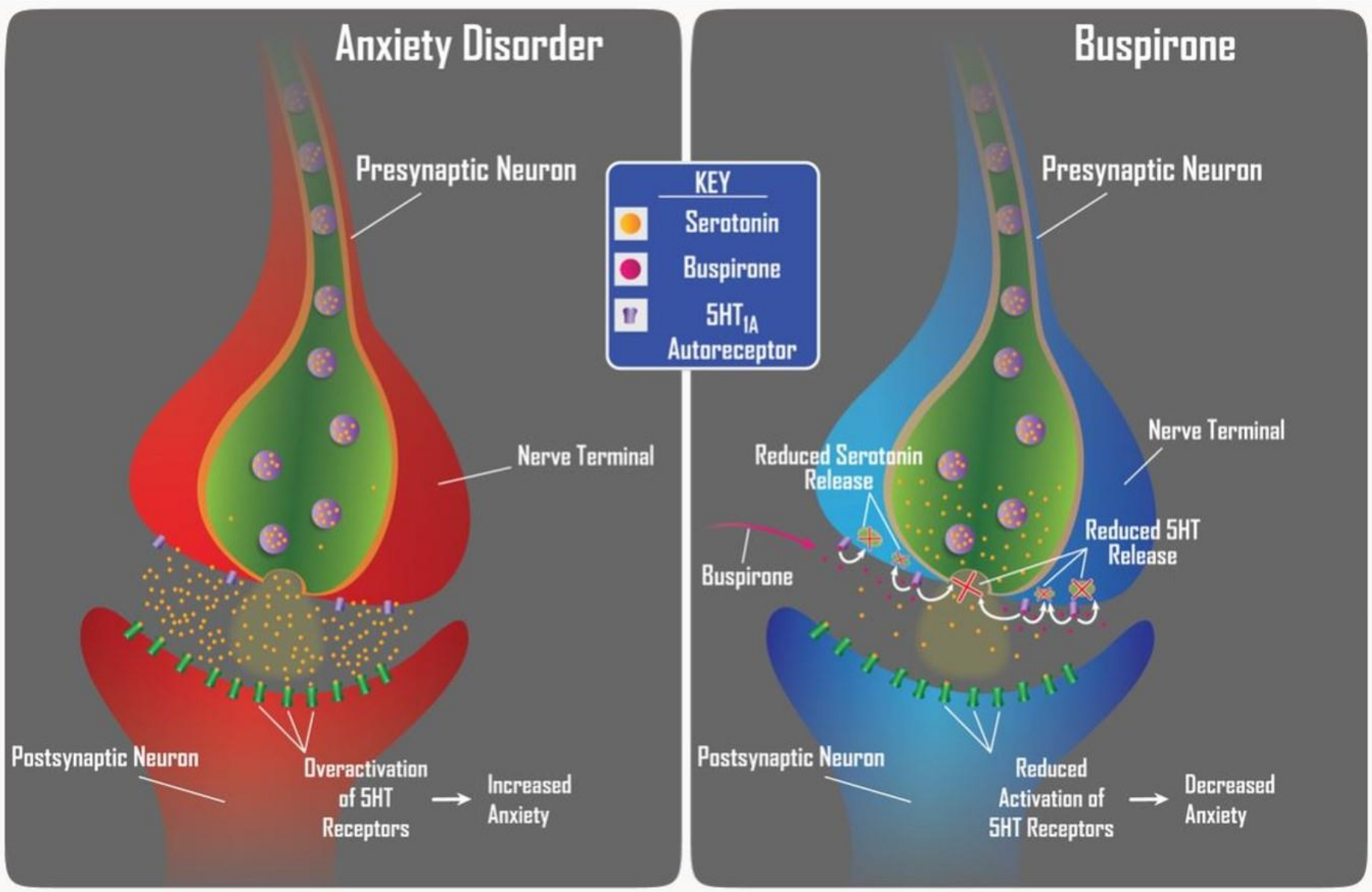


Figure 17.11. Mechanism of Buspirone-Induced Anxiolytic

Original drawing by Nathan Olivier

- **BDZs used as hypnotics can be divided into short- acting and longer-acting.**
- A rapidly eliminated drug (e.g. temazepam) is usually preferred to avoid daytime sedation.
- **A longer-acting drug (e.g. lormetazepam) may be preferred where early morning waking is a problem and where a daytime anxiolytic effect is needed.**
- **Zopiclone, zolpidem and zaleplon are not BZDs but act at BDZ receptors. They have short durations of action and because they are likely to cause less daytime sedation are increasingly popular as hypnotics**.

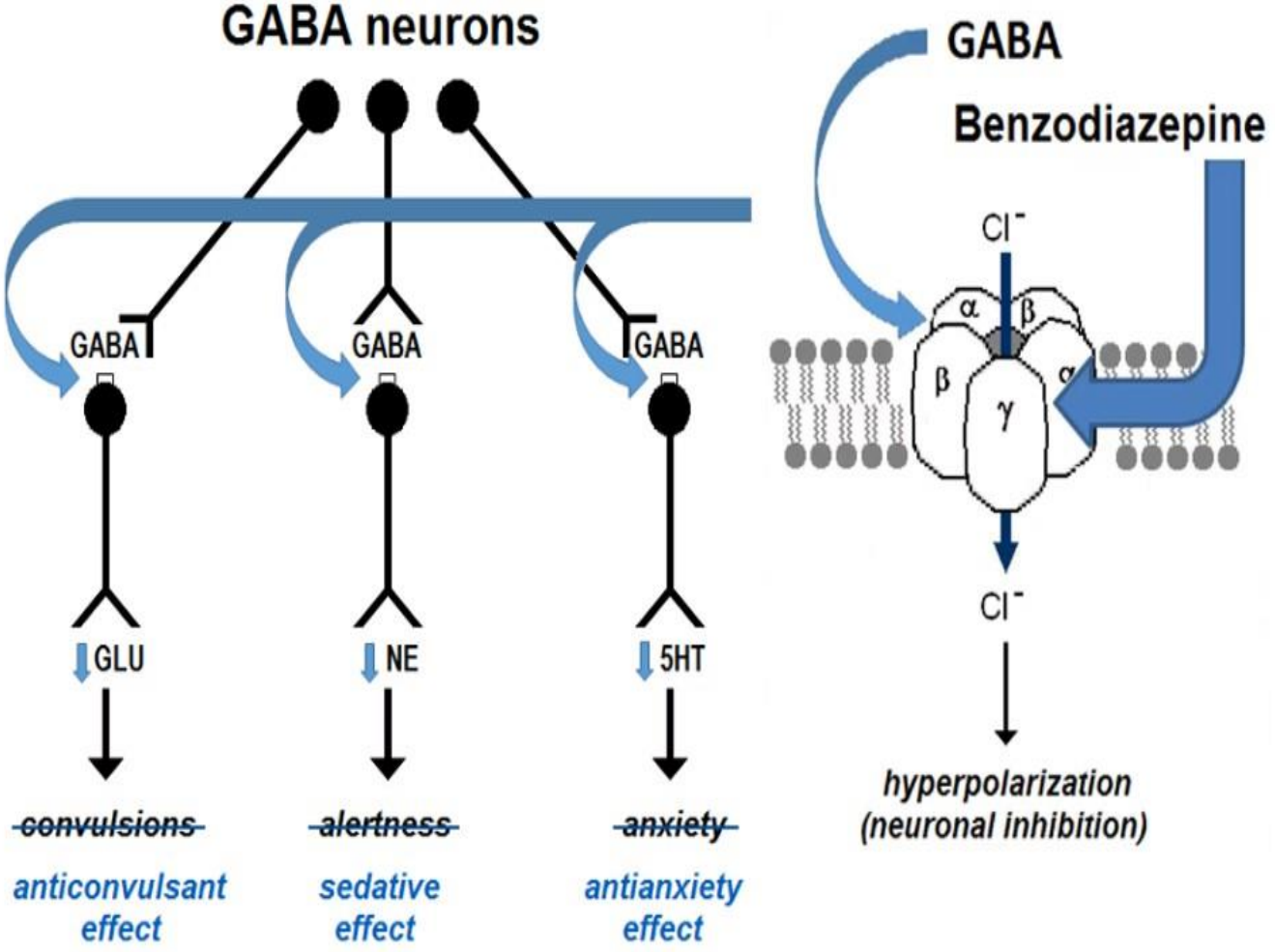


Figure 17.9. GABA Is Mediator of Benzodiazepine-Induced Drug Effects

Original drawing by Raymond M. Quock

- **GABA receptors : the GABA A type are involved in the actions of hypnotics/anxiolytics.**
- **The GABA A receptor belongs to the superfamily of ligand-gated ion channels (other examples are the nicotinic, glycine and 5HT3 receptors).**
- **The GABA A receptor consists of five subunits . Variants of each of these subunits have been cloned (six α-, four β-, three γ- and one δ-subunit).**

Barbiturate receptor Barbiturates (and chloral hydrate and chlormethiazole) are far more depressant than BDZs, because at higher doses they increase the Cl− conductance directly and decrease the sensitivity of the neuronal post synaptic membrane to excitatory transmitters.

Barbiturates readily lead to dependence and relatively small over dosages may be fatal.

Barbiturates (e.g. thiopental) retain a role in anaesthesia and are still used as anticonvulsants (e.g. phenobarbital).

Benzodiazepines also replaced barbiturates for antianxiety use. Ideally, an anxiolytic should be able to provide an antianxiety effect without producing significant sedative side effects. This was part of the issue with barbiturates. Benzodiazepines were an improvement because, at doses that would produce the same antianxiety effect, benzodiazepines produced less sedative side effects compared to barbiturates

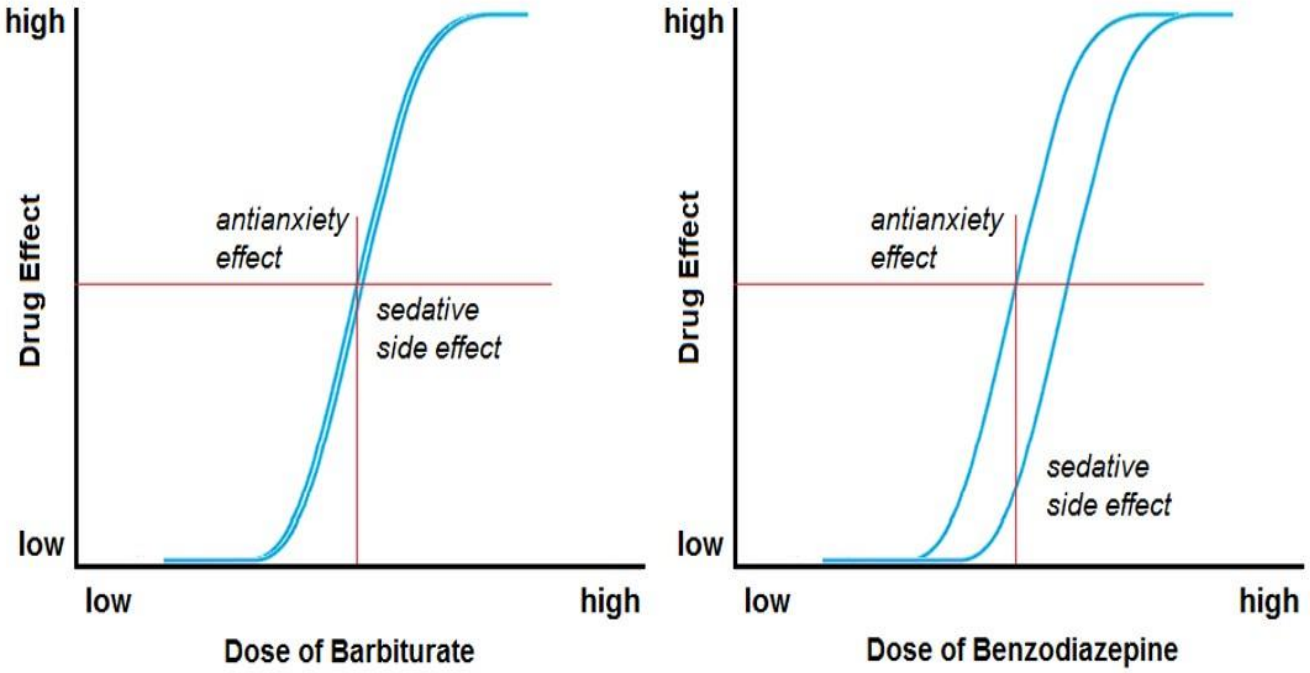


Figure 17.7. Comparison of Anxiolytic Effects of Barbiturates and Benzodiazepines

Original drawing by Raymond M. Quock

Benzodiazepines quickly replaced barbiturates as the preferred sedative-hypnotic drugs because they showed improved drug safety. Benzodiazepines have a lower ceiling effect than barbiturates. At therapeutic doses, benzodiazepines entirely lack the respiratory depressant effects of barbiturates, which contributed to the risk of a fatal overdose

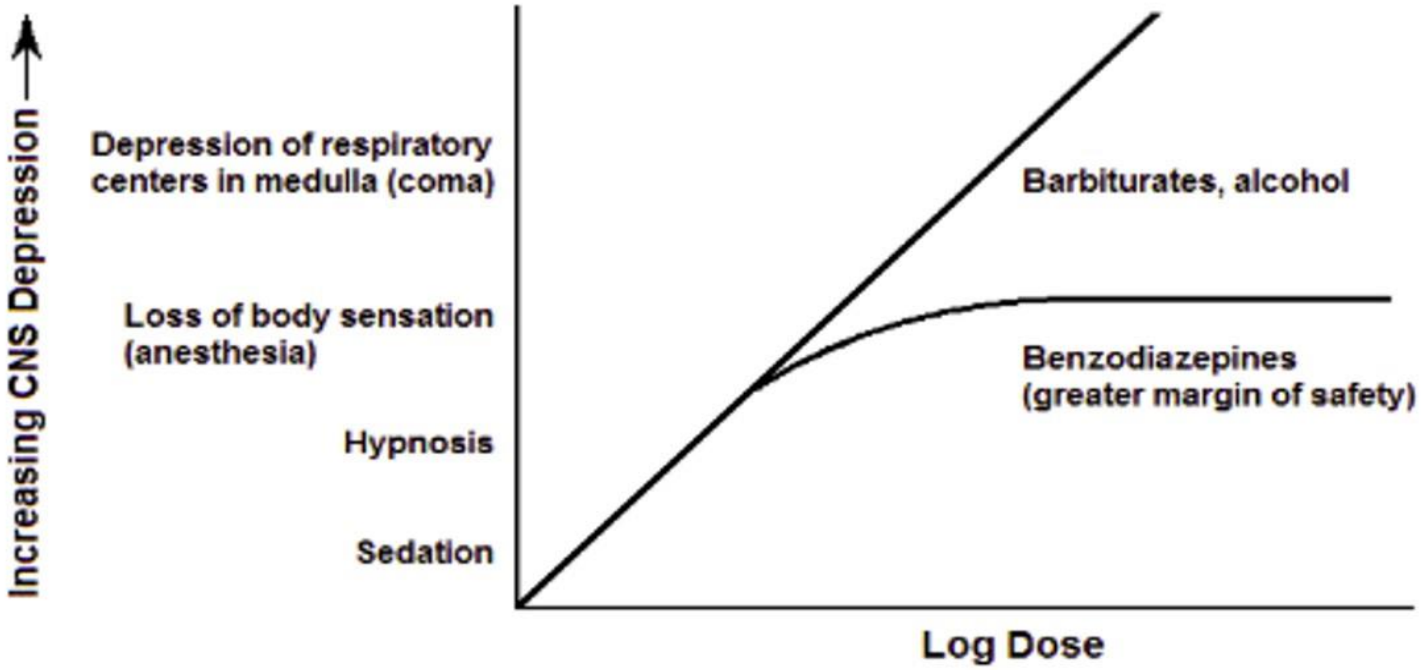


Figure 17.6. Comparison of Barbiturate- and Benzodiazepine-Induced CNS Depression

Original drawing by Raymond M. Quock

Benzodiazepines (BDZs) These are active orally and, although most are metabolized by oxidation in the liver, they do not induce hepatic enzyme systems.

They are central depressants but, in contrast to other hypnotics and anxiolytics, their maximum effect when given orally does not normally cause fatal, or even severe, respiratory depression.

However, respiratory depression may occur in patients with bronchopulmonary disease or with intravenous administration.

Adverse effects include drowsiness, impaired alertness, agitation and ataxia, especially in the elderly.

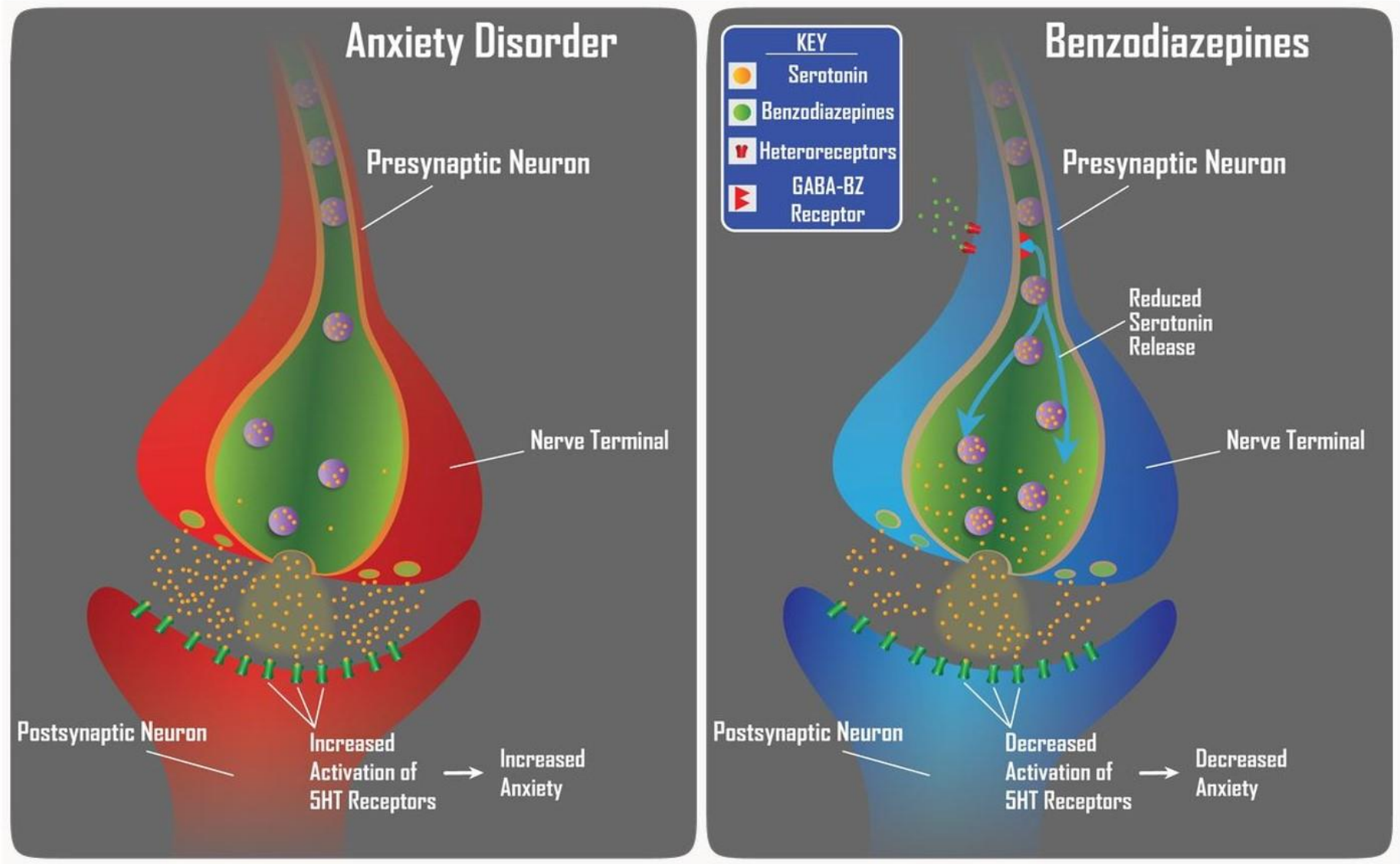


Figure 17.10. Mechanism of Benzodiazepine-Induced Anxiolysis

Original drawing by Nathan Olivier

Dependence

A physical withdrawal syndrome may occur in patients given BDZs for even short periods.

The symptoms, which may persist for weeks or months, include anxiety, insomnia, depression, nausea and perceptual changes.

Drug interactions. BDZs have additive or synergistic effects with other central depressants such as alcohol, barbiturates and antihistamines.

Intravenous BDZs (e.g. diazepam, lorazepam) are used in status epilepticus and very occasionally in panic attacks (however, oral alprazolam is probably more effective for this latter purpose and is safer). Midazolam, unlike other BDZs, forms water soluble salts and is used as an intravenous sedative during endoscopic and dental procedures. **Intravenous BDZs may cause respiratory depression, and assisted ventilation may be required.** **Zopiclone, zolpidem and zaleplon, so called Z-drugs, have shorter half-lives than the BDZs.**

- **Antidepressants:** **Antidepressants, especially specific serotonin reuptake inhibitors (SSRIs) are used in the treatment of most types of chronic anxiety disorders.**
- **Antidepressants have a slow onset and may increase anxiety for several weeks before beneficial effects are seen.**

The serotonergic neurons release transmitter into the synapse, where they then activate 5-HT receptors on the postsynaptic neuron (left panel above and upper panel below). Overactivation of these 5-HT receptors is thought to be linked with increased levels of anxiety

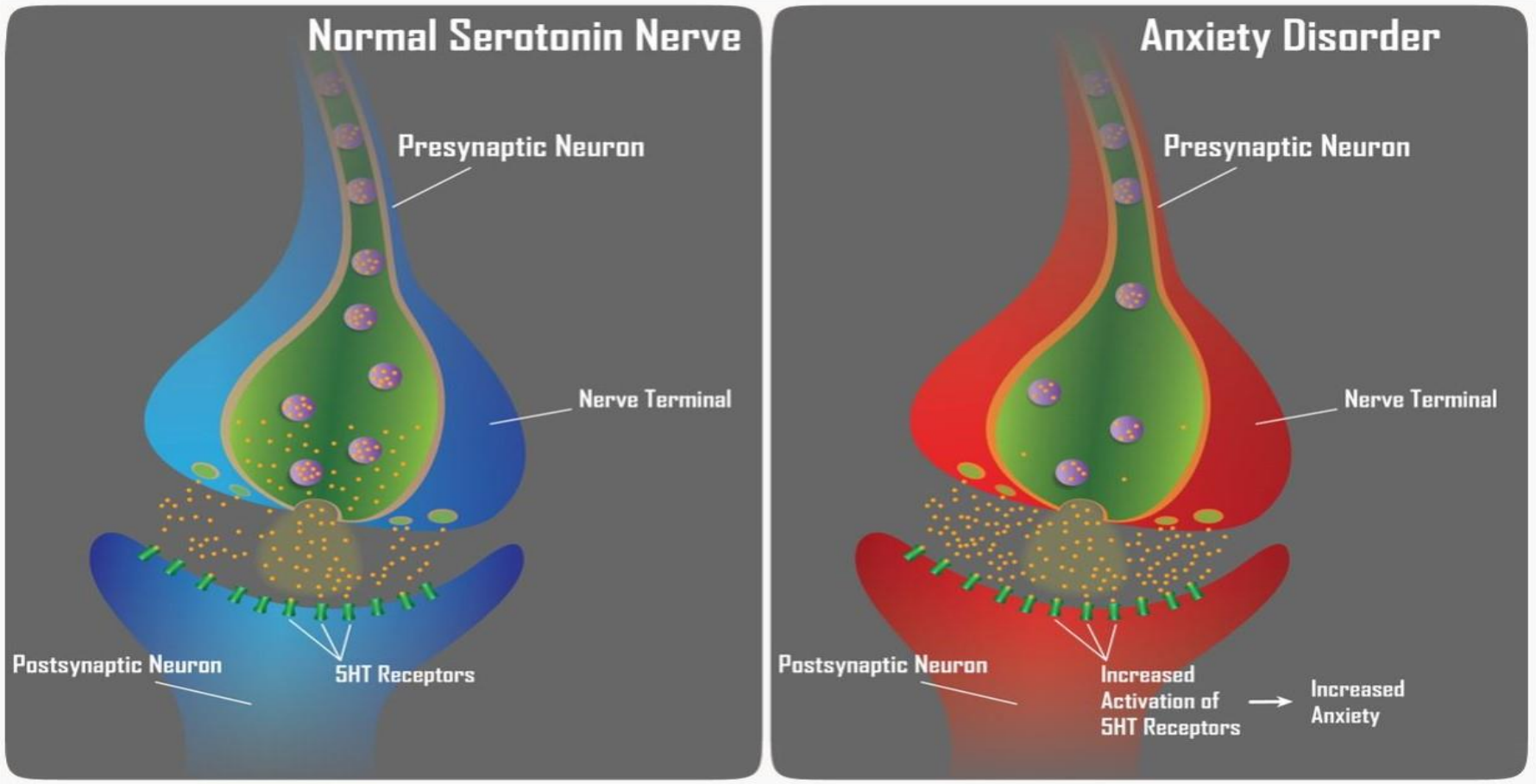


Figure 17.4. Serotonin Hypothesis of Anxiety Disorders

Original drawing by Nathan Olivier

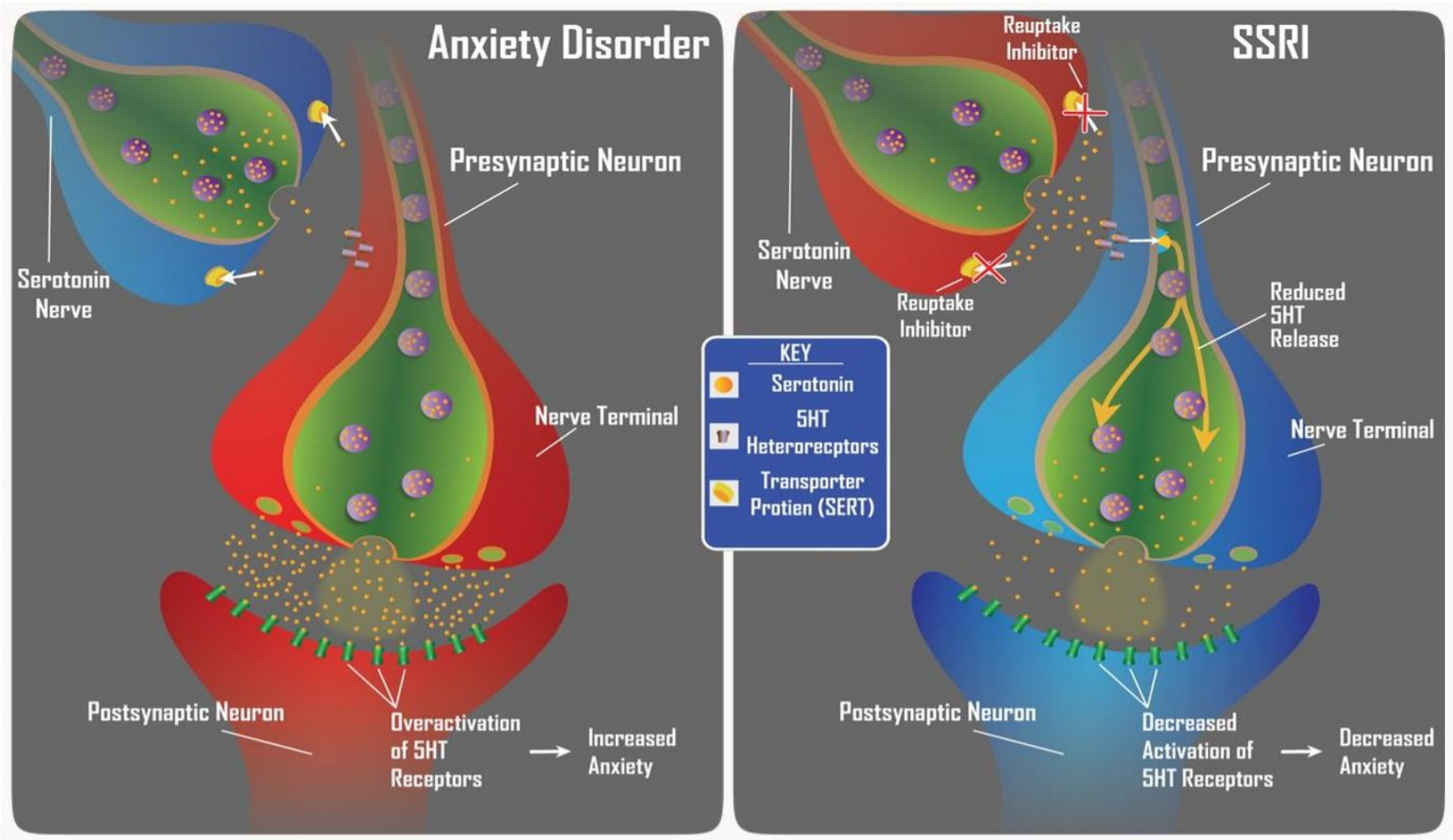


Figure 17.12. Mechanism of Action of SSRI-Induced Anxiolytic Effect

Original drawing by Nathan Olivier


THANK YOU
FOR LISTENING