# BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

## Programme: M.Sc., Biomedical Science

**Course Title : Pharmacology and Toxicology**

**Course Code : BM35C7**

## Unit-2

## Neuropharmacology - Part 1

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**Guest Lecturer**

**Department of Biomedical Science**

# PHARMACOLOGY

UNIT II

# The cardinal features of general anaesthesia are:

Loss of all sensation, especially pain

Sleep (unconsciousness) and amnesia

Immobility and muscle relaxation

Abolition of somatic and autonomic reflexes.

## CLASSIFICATION

### Inhalational

*Gas*
- Nitrous oxide

*Volatile liquids*
- Ether
- Halothane
- Enflurane
- Isoflurane
- Desflurane
- Sevoflurane

### Intravenous

*Inducing agents*
- Thiopentone sod.
- Methohexitone sod.
- Propofol
- Etomidate

*Slower acting drugs*

*Benzodiazepines*
- Diazepam
- Lorazepam
- Midazolam

*Dissociative anaesthesia*
- Ketamine

*Opioid analgesia*
- Fentanyl

Cyclopropane, trichloroethylene and methoxyflurane are no longer used.

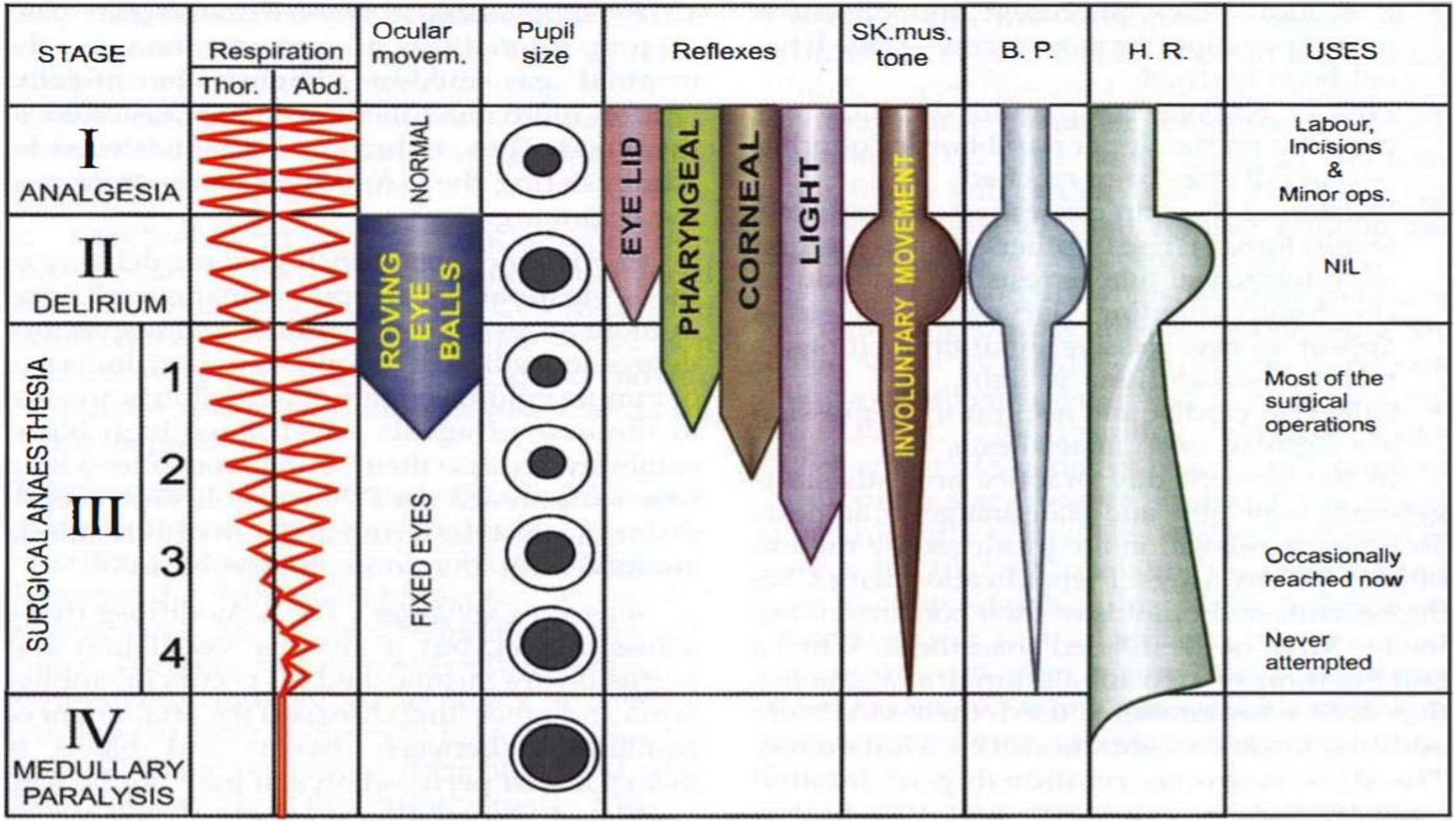



**Fig. 27.1:** Stages of general anaesthesia

# Properties of an ideal anaesthetic

For the patient It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

For the surgeon It should provide adequate analgesia, immobility and muscle relaxation.

For the anaesthetist Its administration should be easy, controllable and versatile. It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.

# PHARMACOKINETICS

# PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS

Depth of anaesthesia depends on the potency of the agent

(MAC is an index of potency) and its partial pressure (PP) in the brain,

while induction and recovery depend on the rate of change of PP in the brain

**FACTORS AFFECTING THE PP OF ANAESTHETIC ATTAINED IN THE BRAIN**

**PP OF ANAESTHETIC IN THE INSPIRED GAS**

**PULMONARY VENTILATION**

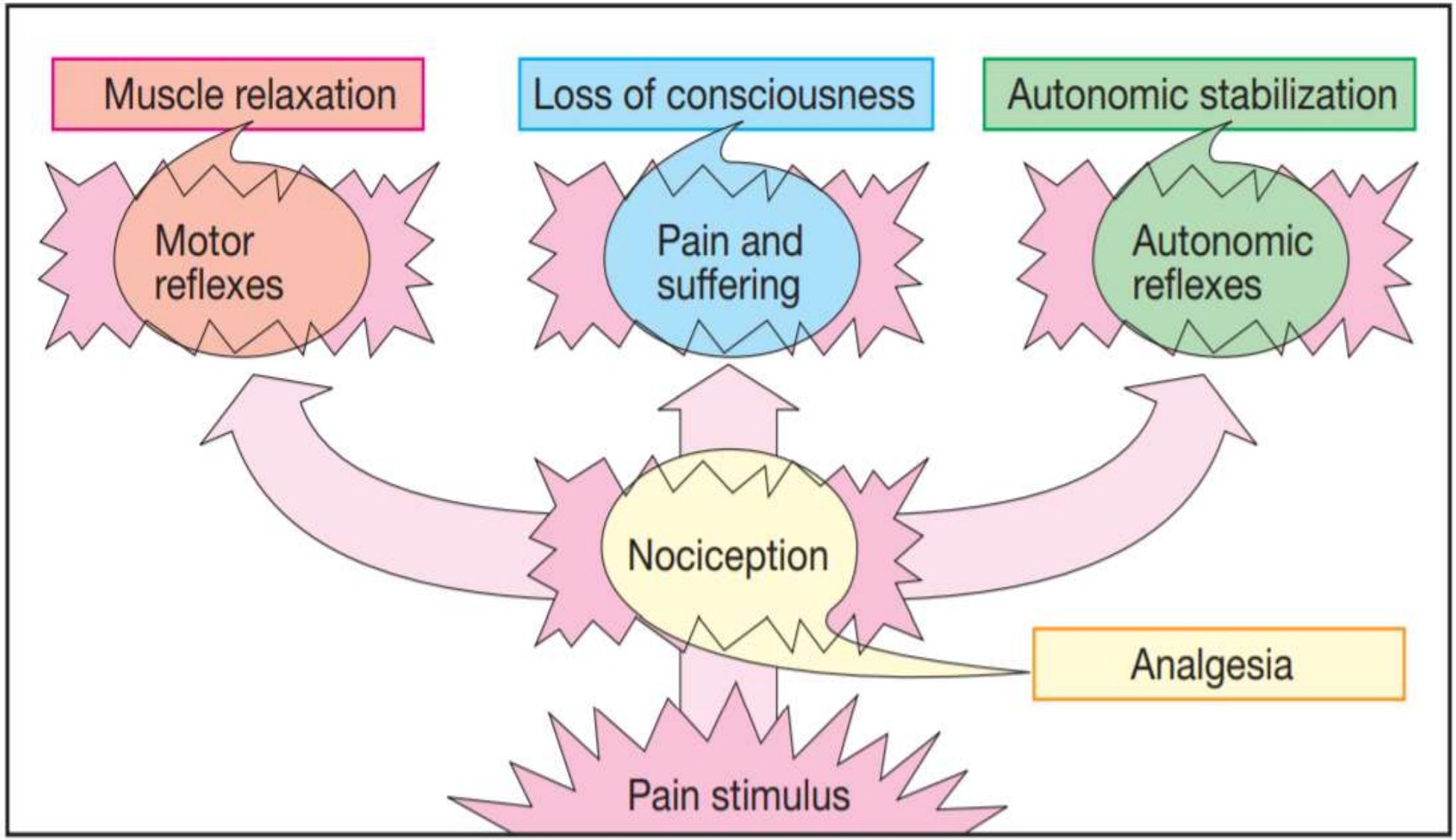
**ALVEOLAR EXCHANGE**

**SOLUBILITY OF ANAESTHETIC IN BLOOD**

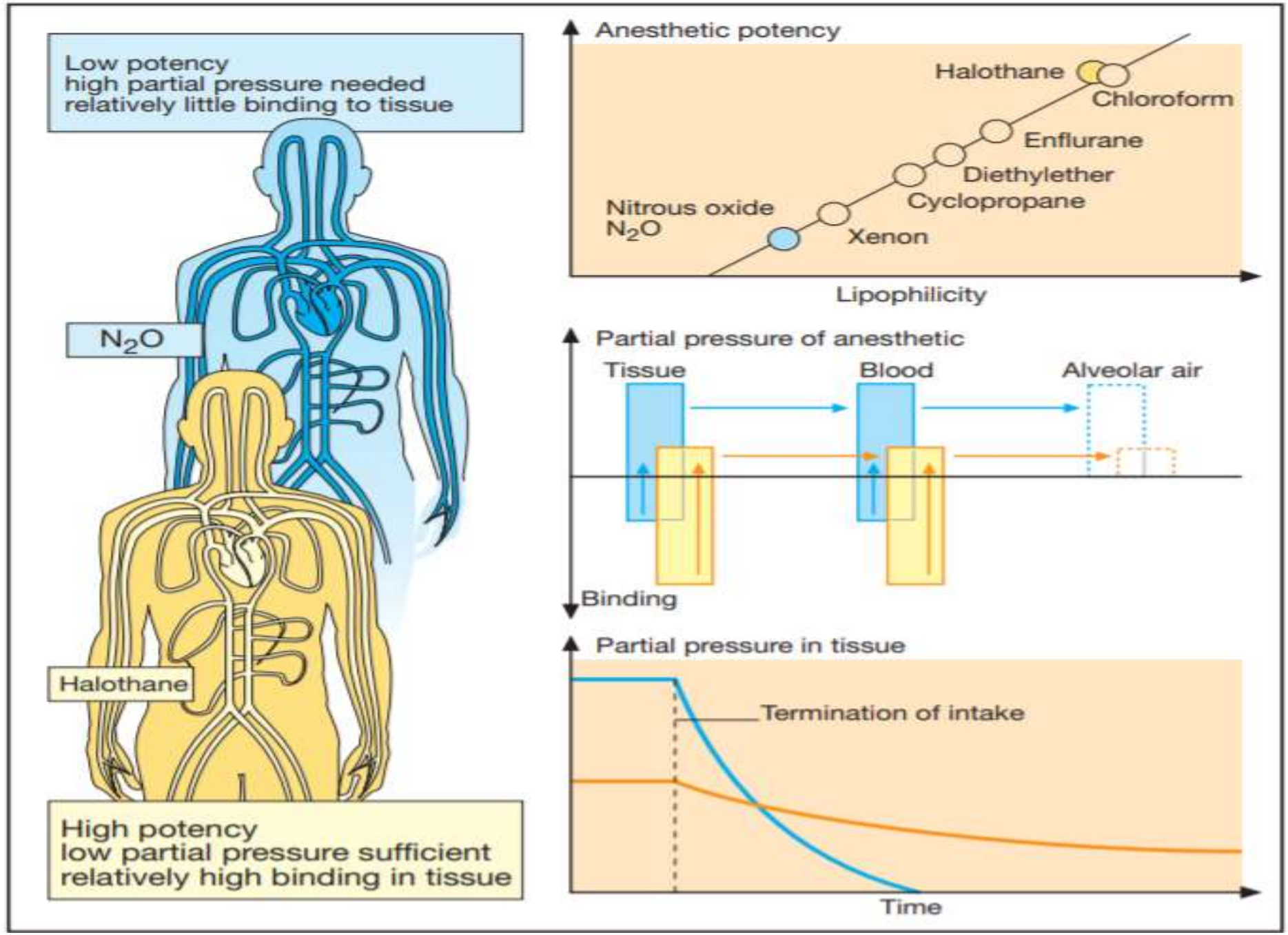
**SOLUBILITY OF ANAESTHETIC IN TISSUES**

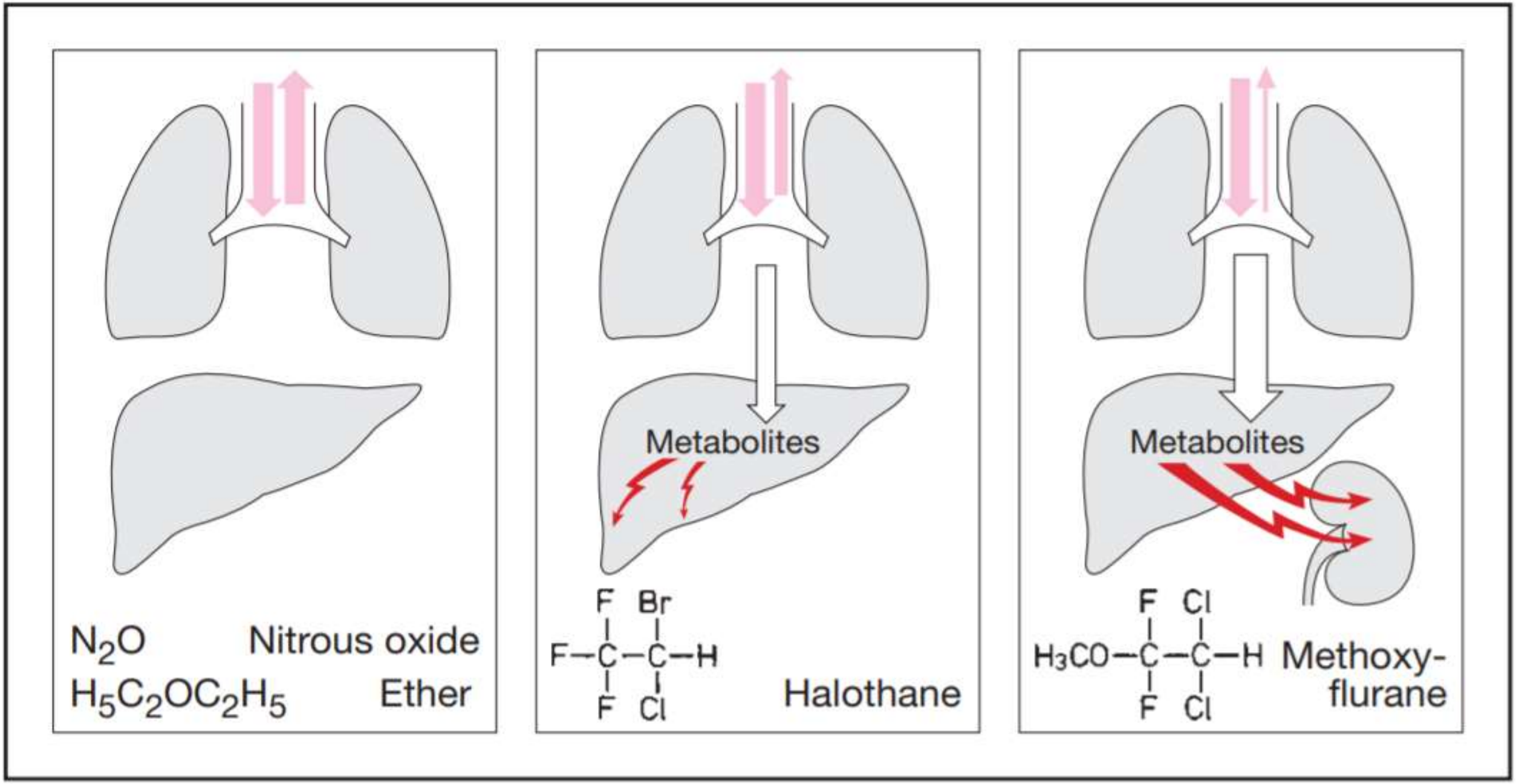
**CEREBRAL BLOOD FLOW**

**ELIMINATION**




**A. Goals of surgical anesthesia**


Low potency
high partial pressure needed
relatively little binding to tissue
$N_2O$
Halothane
High potency
low partial pressure sufficient
relatively high binding in tissue
Anesthetic potency
Halothane
Chloroform
Enflurane
Diethylether
Cyclopropane
Nitrous oxide
$N_2O$
Xenon
Lipophilicity
Partial pressure of anesthetic
Tissue
Blood
Alveolar air
Binding
Partial pressure in tissue
Termination of intake
Time




**B. Elimination routes of different volatile anesthetics**

# NITROUS OXIDE

- Colourless, inorganic gas with a sweet taste.
- It does not undergo significant decomposition in the body.
- If administered along with air, stage of excitement and delirium and amnesia.
- Used together with oxygen and other agents such as isoflurane.
- Analgesia when inhaled in the concentration of 35 to 40% with air.
- Loss of consciousness occurs with the concentration of 65 to 70%
- Surgical anaesthesia can be reached with an 80:20 (nitrous oxide and oxygen)
- Further increase in the concentration of the anaesthetic agent produces hypoxia.
- No serious, deleterious effects on circulation, respiration, liver and kidneys
- Safest anaesthetic agent.

# Mechanism of Action

- Nitrous oxide has multiple supraspinal and spinal targets.
- The anesthetic effect of nitrous oxide is through non-competitive **NMDA inhibition** in the central nervous system.
- The analgesic effects occur by **releasing endogenous opioids** that act on opioid receptors; its analgesic actions are like morphine.

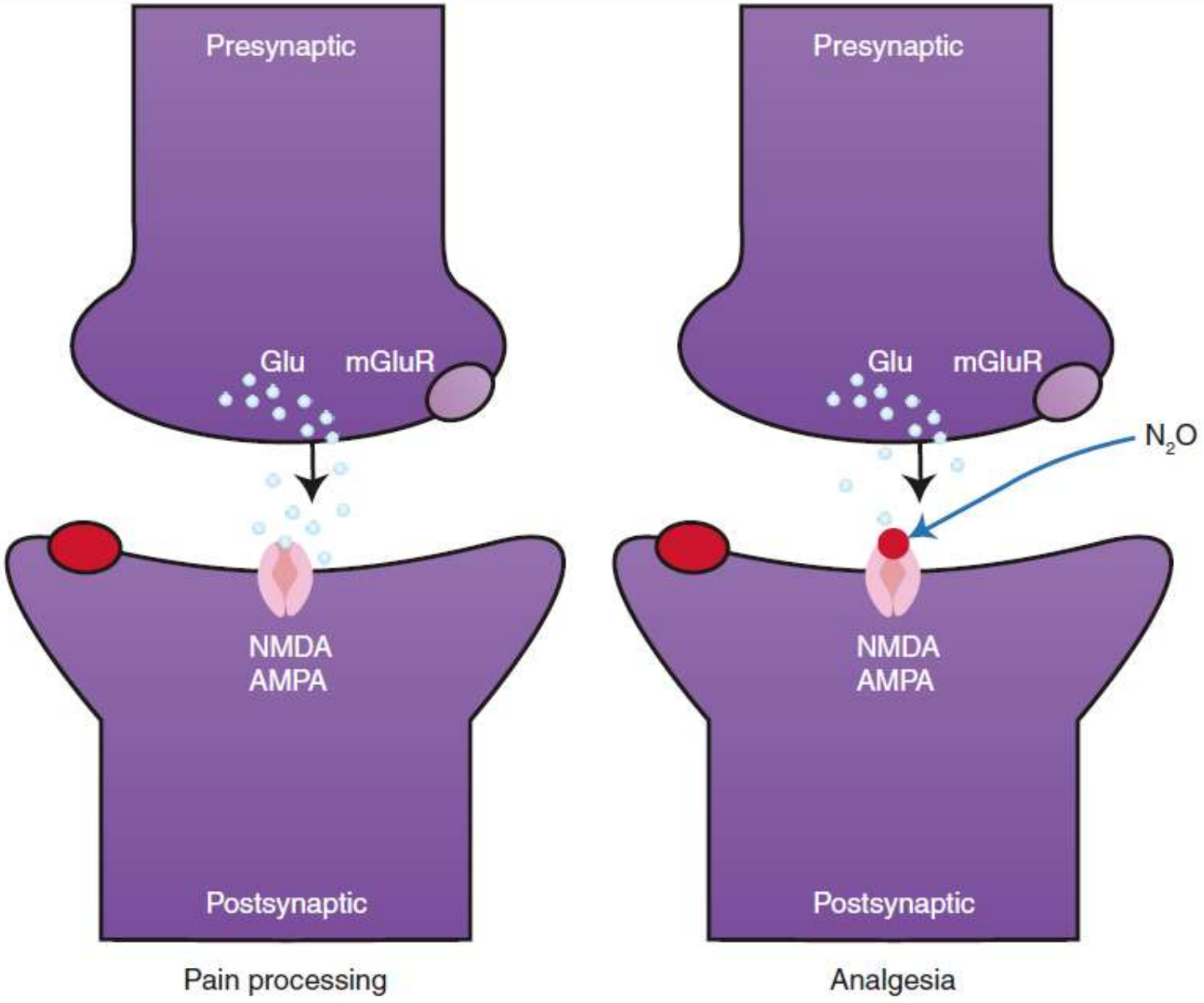



**Fig. 3.5** Nitrous oxide is responsible for blocking glutaminergic (pain stimulatory) receptors in substantia gelatinosa, thereby causing analgesia

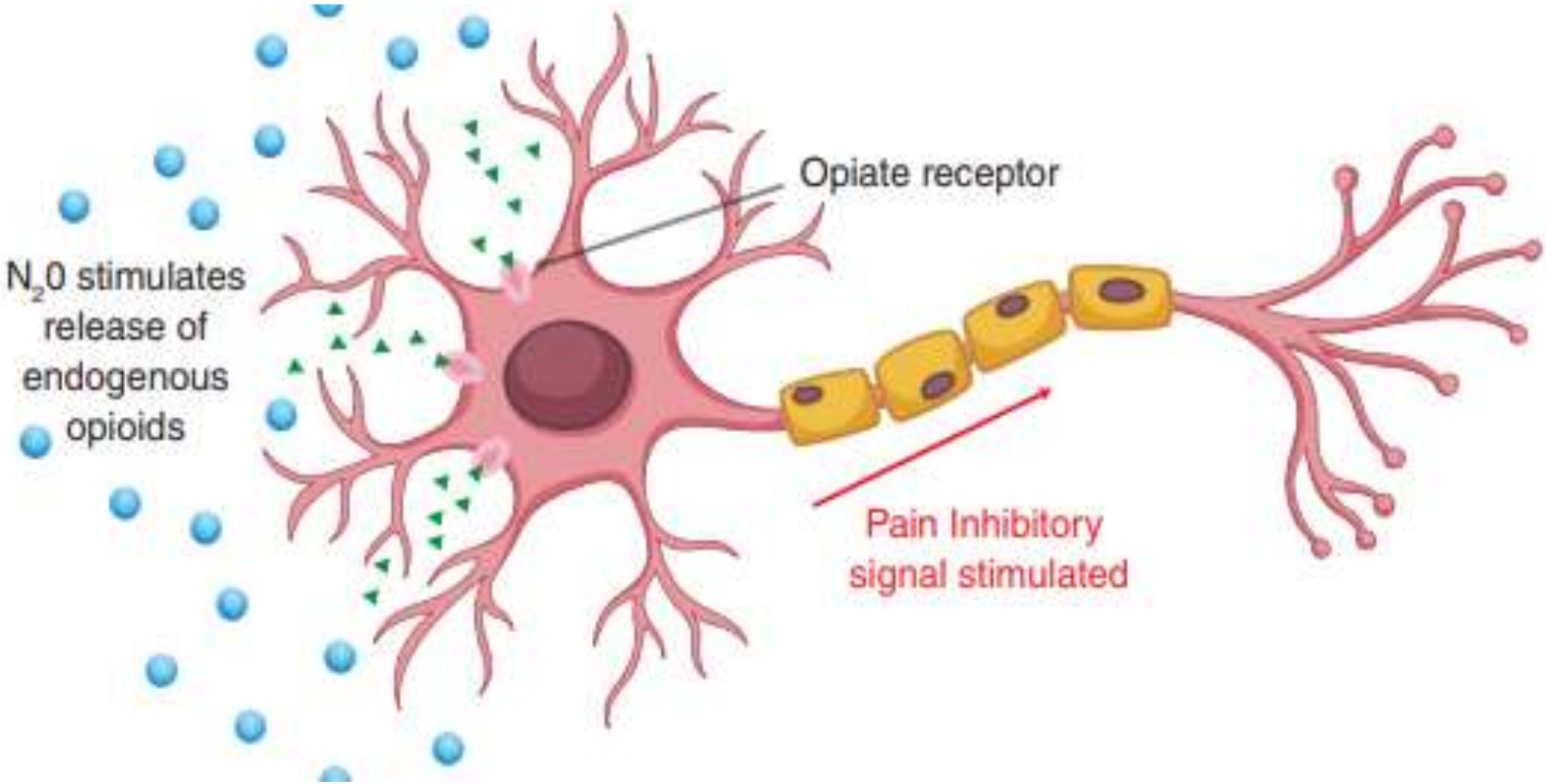
## Role of Glutamate

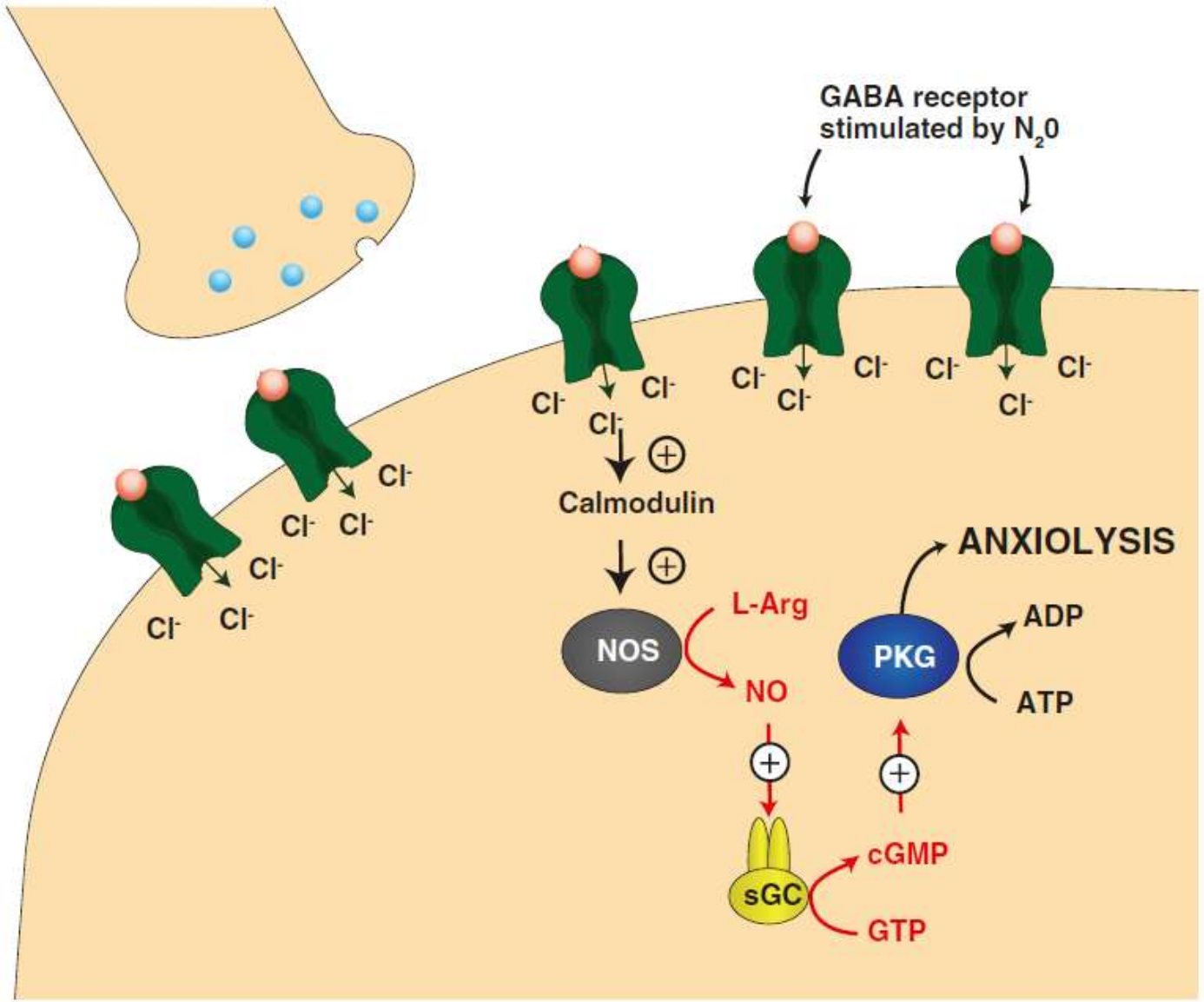
Fifty percent of nitrous oxide blocks both NMDA and AMPA glutaminergic receptors
in the substantia gelatinosa of the dorsal horn of the spinal cord, an area of the cord that is known to be intimately involved in pain processing

It is possible that glutaminergic neurons are also involved in nitrous oxide analgesia

- A amino 3 hydroxy 5methyl 4 isoxazolepropionic acid receptor
- N-Methyl D Aspartate receptor.

The opioid system was the first neurotransmitter system to be identified as being involved in the analgesic actions of nitrous oxide






*N2O activates the benzodiazepine binding site of the GABAA receptor, since flumazenil blocks nitrous oxide anxiolysis.*

*This facilitates the binding of g-aminobutyric acid resulting in an influx of Cl-, which causes activation of calmodulin.*

*Calmodulin in turn activates nitric oxide synthase, which catalyzes the conversion of L-arginine to L-citrulline with the liberation of nitric oxide.*

*Nitric oxide then stimulates enzyme soluble guanylyl cyclase, resulting in the production of the second messenger cyclic guanosine monophosphate [cGMP].*

*cGMP then stimulates a cyclic GMP-dependent protein kinase [PKG] resulting in anxiolysis*

# Absorption, fate and excretion:

- Nitrous oxide is not altered within the body
- Is carried in the form of a physical solution in the blood.
- It is rapidly eliminated through lungs within 2 to 5 minutes after its withdrawal.

# Advantages:

- Non-inflammable and non-irritant.
- Rapid induction and recovery.
- Analgesic in subanaesthetic concentration; and
- Nausea and vomiting are uncommon.

# Disadvantages

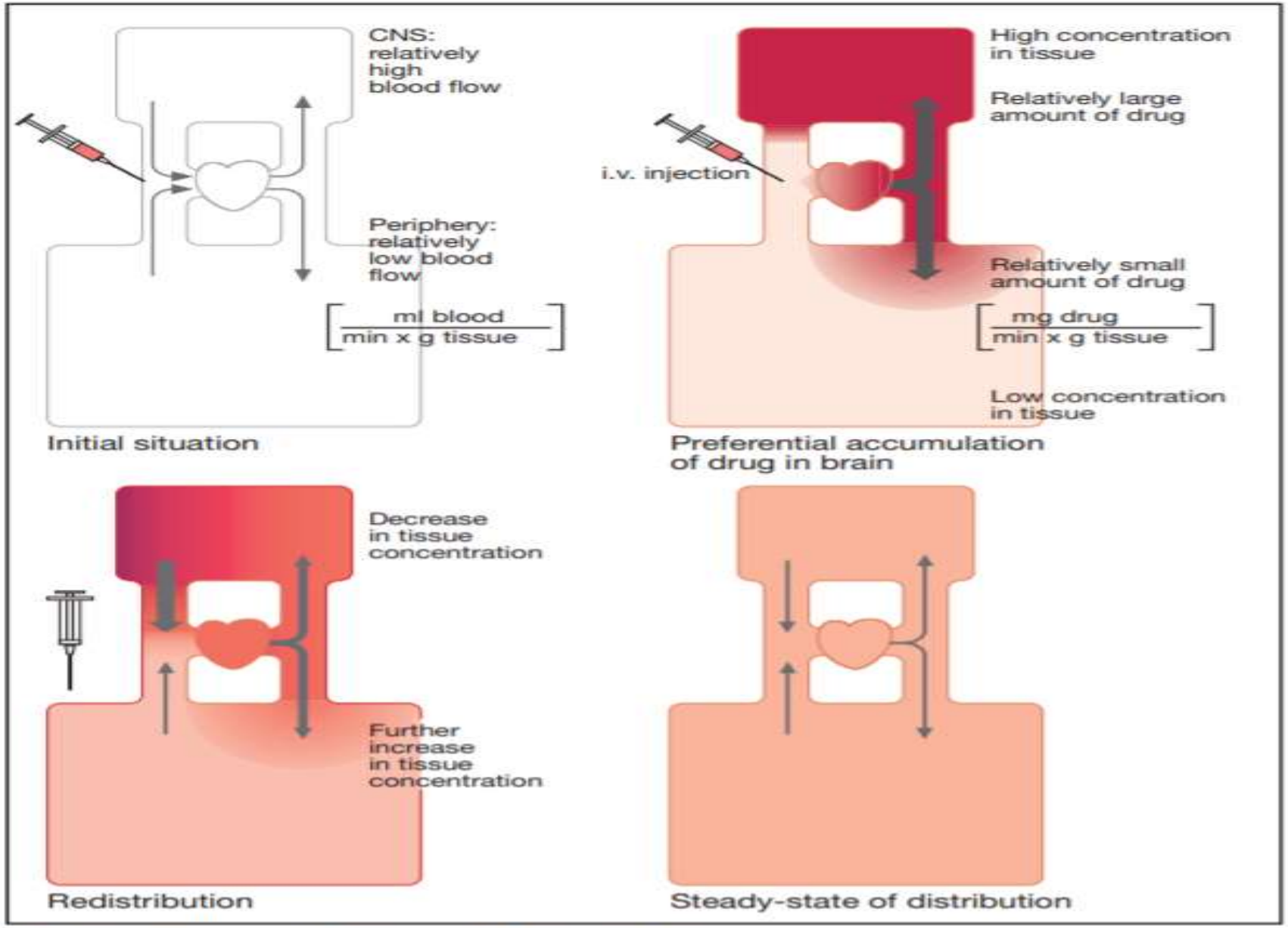
- Not a potent anaesthetic agent by itself; must be supplemented with another preanaesthetic agent or a muscle relaxant.
- Excitement may be violent.
- CO2 accumulation and hypoxia may develop during prolonged use.
- Diffusion hypoxia develops at the time of discontinuation of nitrous oxide and is dangerous in patients with low cardiopulmonary reserve.
- This can be prevented by administration of 100% oxygen
- *An increase in spontaneous abortions has been reported dentists*
- Contraindicated in patients with collections of air in the pleural, pericardial or peritoneal cavities; intestinal obstruction; occlusion of the middle ear; chronic obstructive airway disease; or emphysema.

# Therapeutic uses:

- **It may be used for tooth extraction, obstetric analgesia, and during** painful procedures such as changing dressings in burns patients.
- When nitrous oxide is given in high concentration (70-80%) with another potent inhalational anaesthetic like halothane it facilitates delivery of the latter to blood at a higher rate and helps in achieving faster induction. This effect is termed as **second gas effect.**

# Ether

- Potent anaesthetic,
- Produces good analgesia & muscle relaxation
- By **reducing ACh output** from motor nerve endings –
- Dose of competitive neuromuscular blockers should be reduced to about 1/3.
- It is highly soluble in blood-induction is prolonged and unpleasant
- Breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions).
- Recovery is slow; postanaesthetic nausea, vomiting and retching are marked.




**A. Termination of drug effect by redistribution**

# THIOPENTAL:

- **Thiopental sodium is readily soluble in water but the solution** deteriorates on keeping.
- Solution is intensely alkaline with a pH varying from 10.5 to 11.
- High alkalinity can cause local irritation and venous thrombosis.
- Given IV, it rapidly induces hypnosis and anaesthesia–without analgesia.
- Thiopental, 5-ethyl-5-(1-methylbutyl)2-thiobarbituric acid

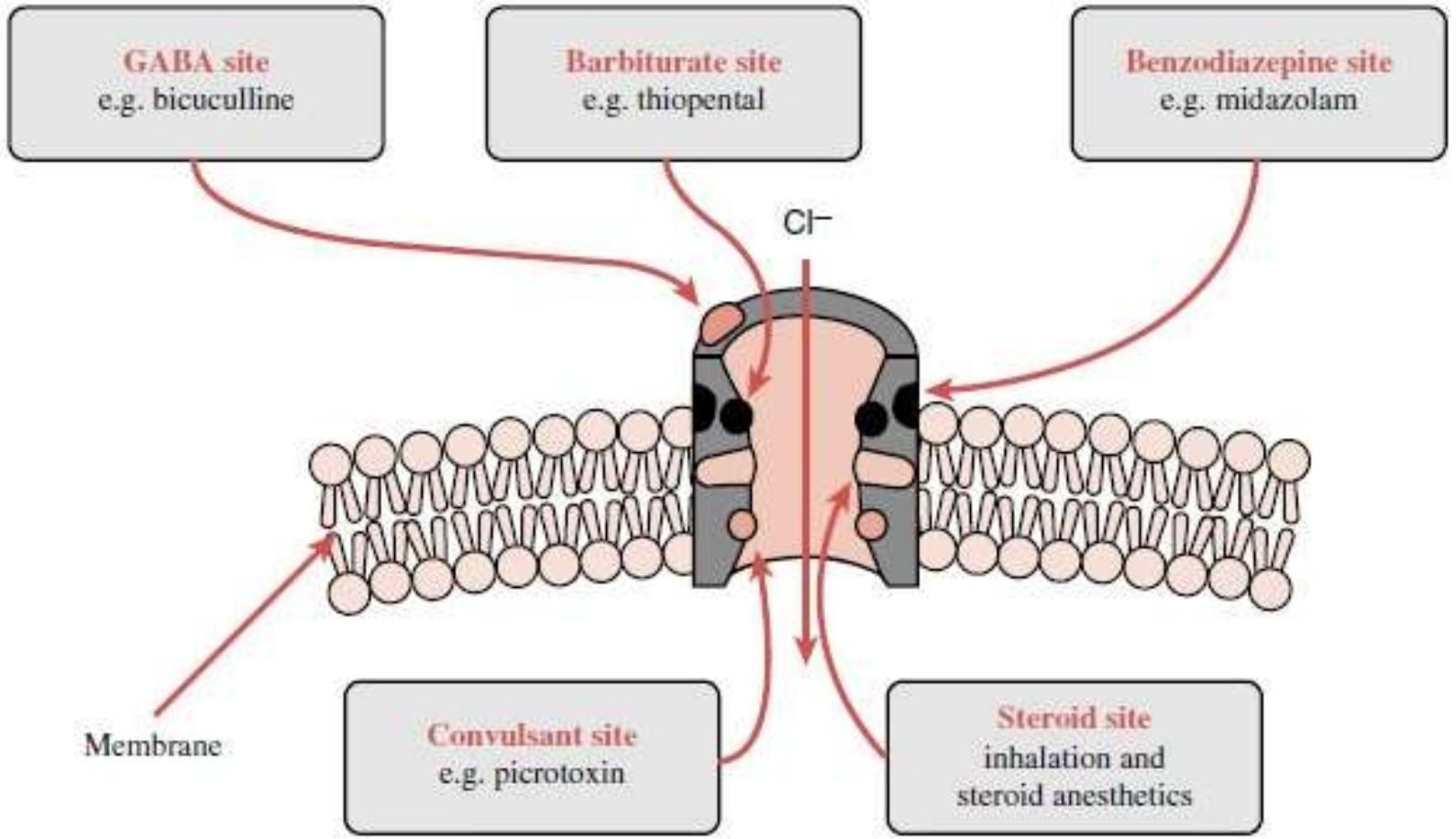



**FIGURE 25.7**
The $GABA_A$-receptor–chloride ionophore sites of drug action.

Its mechanism of action is through potentiation of GABAergic transmission via $GABA_A$ receptor

# Anaesthetic action:

- **The induction is very quick and pleasant.**
- **Consciousness is lost first,** then the reflex activity and muscle tone and lastly, the vital medullary centres are depressed.
- Pupils react to light and remain contracted in light hypnosis.
- The corneal reflex remains active until deep anaesthesia is achieved.
- Cerebral blood flow and cerebral metabolic rate are reduced and there is a marked reduction of intracranial tension.
- It also reduces cerebral metabolism. It is, therefore, a choice for patients with cerebral swelling.
- A fairly reliable sign of an adequate induction by thiopental is the absence of the eyelid reflex.
- Presence of swallowing, phonation and reflex movements of eyes during anaesthesia indicate need for further injection.
- Though the reflexes return in 10-30 minutes, after stoppage the patient remains disoriented for several hours and hence, must not be left alone

# Absorption, fate and excretion:

- **The very short duration of action is attributed to its high lipid solubility.**
- The rapid metabolism of the drug by liver may also contribute to its short duration of action.
- With successive doses, body fat depots get saturated with the drug.
- Slow release of the stored drug back into the plasma is responsible for the prolonged recovery and continuation of drowsiness observed after the cessation of anaesthesia.
- Thiobarbiturates readily cross the placental barrier and appear in breast milk.

# COMPLICATIONS OF GENERAL ANAESTHESIA

**DURING ANAESTHESIA**

Respiratory depression and hypercarbia.

Salivation, respiratory secretions-less

Cardiac arrhythmias, asystole.

Fall in BP

Aspiration of gastric contents: acid pneumonitis.

Laryngospasm and asphyxia.

Delirium, convulsions

# INTRAVENOUS ANAESTHETICS INDUCING AGENTS

- These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (-11 sec)
- Generally used for induction because of rapidity of onset of action.
- Anaesthesia is then usually maintained by an inhalational agent.
- They also serve to reduce the amount of maintenance anaesthetic.
- Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

# SLOWER ACTING DRUGS

- Benzodiazepines (BZDs)
- In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for **'conscious sedation'**.
- BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc.
- Anaesthetic action of BZDs can be rapidly reversed by **flumazenil 0.5-2 mg i.v.**

# SEDATIVE- HYPNOTIC

- Sedative

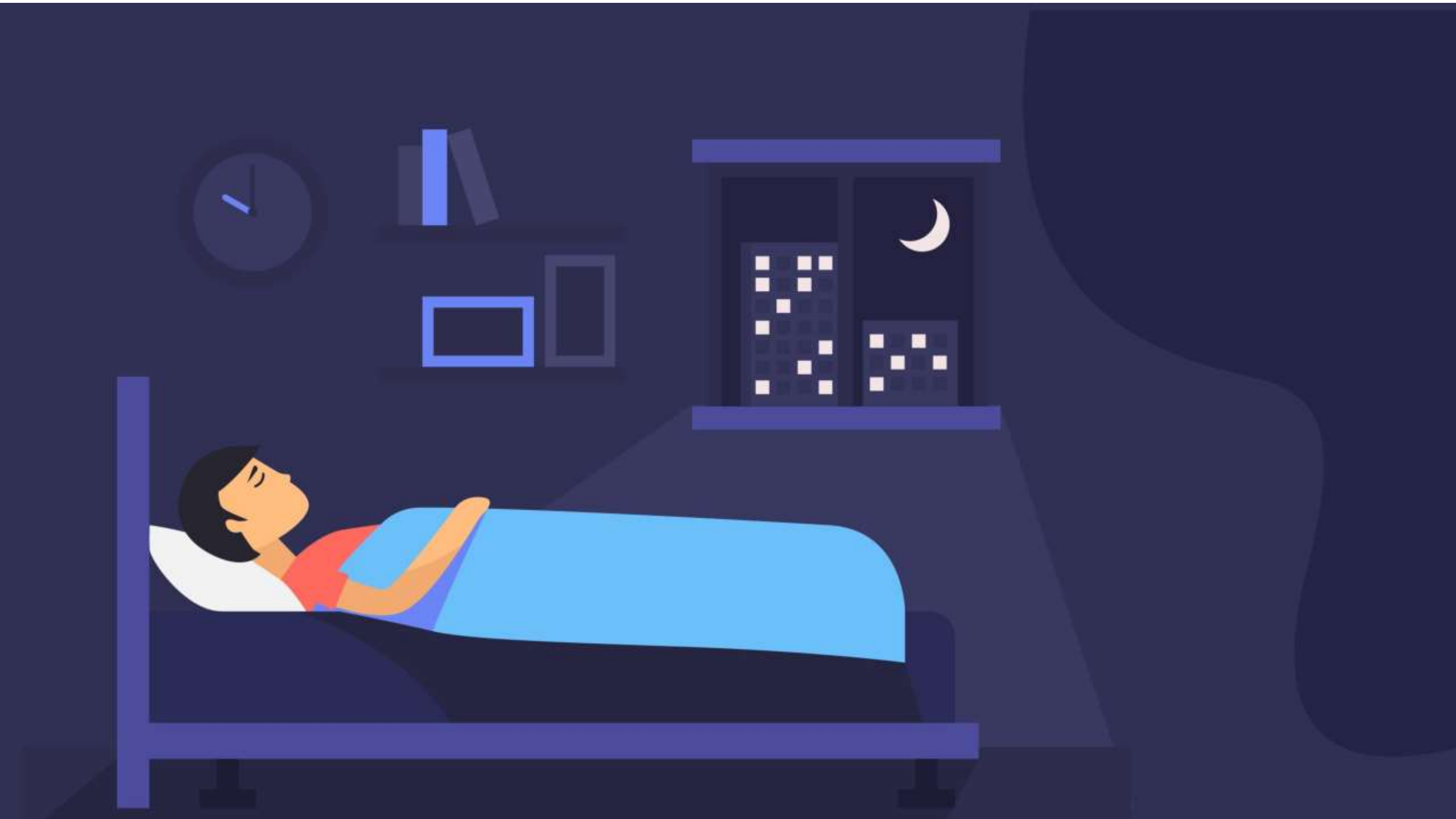
  A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced.

  Decreased responsiveness to any level of stimulation;

  Decrease in motor activity and ideation.

- Hypnotic

  A drug that induces and/or maintains sleep, similar to normal arousable sleep.



Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1-4-REM are repeated cyclically.

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The EEG waves have been divided into---

α: high amplitude, 8–14 c.p.s. (cycles per second)
β: low amplitude, 15–35 c.p.s.
θ: low amplitude, 4–7 c.p.s.
δ: high amplitude, 0.5–3 c.p.s.

K complex: deep negative wave followed by positive wave and a few spindles.

During sleep, the brain generates a patterned rhythmic activity that can be monitored by means of the electroencephalogram (EEG).

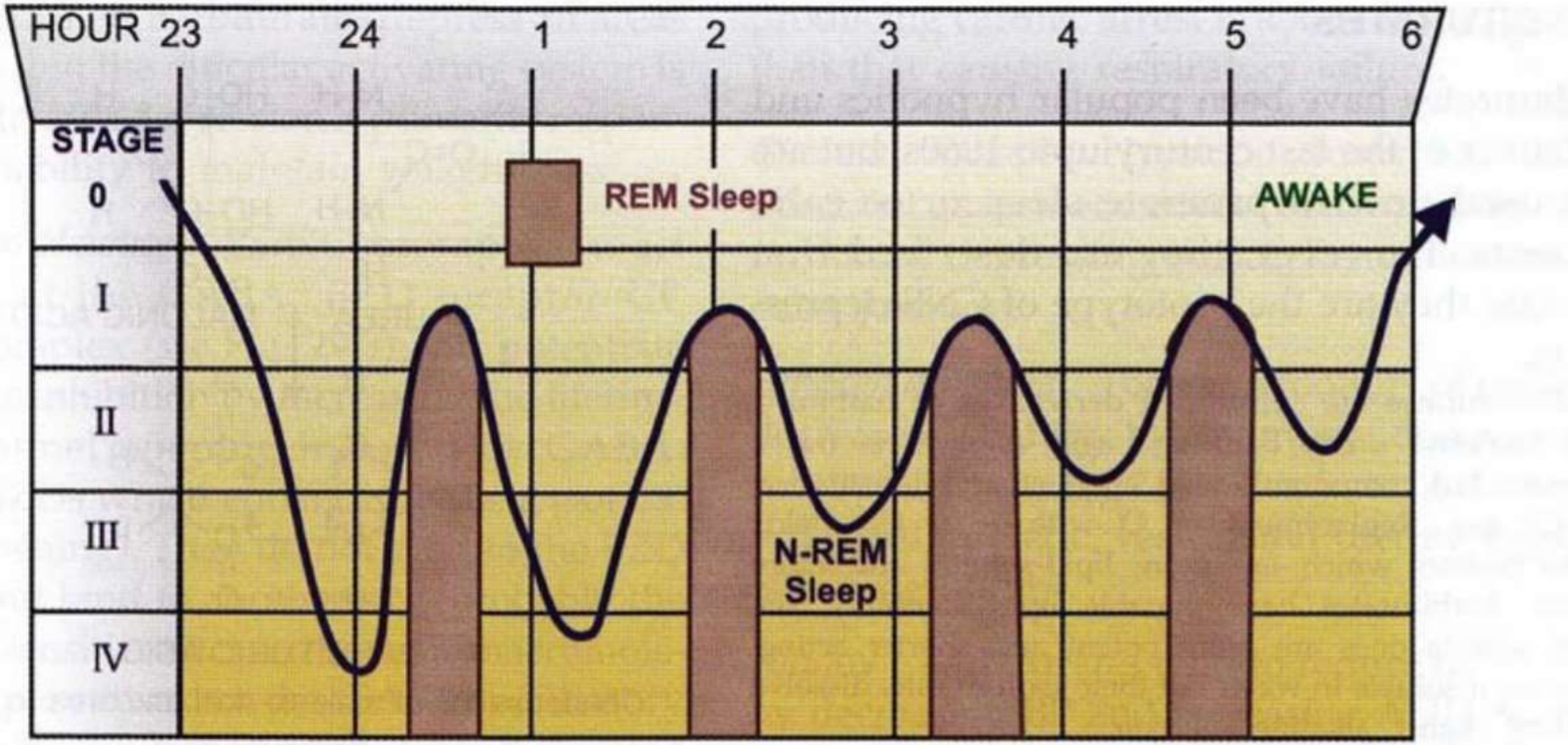



**Fig. 29.1:** A normal sleep cycle

# Sleep is an architectured cyclic process

- Stage (Awake)

  From lying down to falling asleep,

  1-2% of sleep time. EEG shows α.

  Eye movements are irregular or slowly rolling.

- Stage 1 (Dozing)

  α activity is interspersed with o waves.

  Eye movements are reduced

  3-6% of sleep time.

- Stage 2 (Unequivocal sleep)

  0 waves with interspersed spindles, K complexes;

  little eye movement; subjects are easily arousable.

  40-50% of sleep time.

- Stage 3 (Deep sleep transition)

  EEG shows 8, 0 and spindle activity, K complexes

  Eye movements are few

  Subjects are not easily arousable;

  Comprises 5-8% of sleep time.

- Stage 4 (Cerebral sleep)

  8 activity predominates in EEG, K complexes cannot be evoked. Eyes are practically fixed; subjects are difficult to arouse.

  Night terror may occur at this time.

  It comprises 10--20% of sleep time.

- While falling asleep,
    Stages 1, 2, 3 and 4 of NREM sleep.
    After about 90-120 minutes of NREM sleep,
    REM sleep occurs, lasting for 5-30 minutes.
- In general,
    NERM stages 1 and 2 constitute 50-60%,
    NREM stages 3 and 4 (slow wave) 15 to 25%
    REM 20-25% of total sleep in young adults.

Slow wave sleep is prominent in children

Decreases with the age Absent in healthy old people

| NREM | REM |
| --- | --- |
| Sleep is very peaceful<br>With preponderance of the parasympathetic activity | Sleep is not so restful<br>Sympathetic activity predominates during REM sleep.; |
| Dreaming is infrequent and the dreams are rarely recalled on awakening | 75% of the dreams occur in this type of sleep; the dreams tend to be more vivid, bizarre |
| Diminution of the metabolic rate, heart rate, cardiac output and peripheral vascular resistance. | Dreams are accompanied by cardiovascular responses to the dream activities such as running or escaping. The heart rate, BP, cardiac output, peripheral vascular resistance rise markedly. Central apnoea |

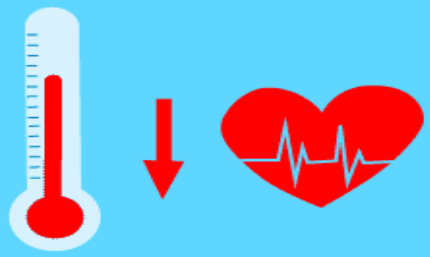
# The 4 Stages of Sleep

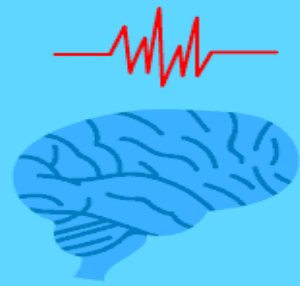
## NREM Stage 1

- transition period between wakefulness and sleep
- lasts around 5 to 10 minutes

## NREM Stage 3

- muscles relax
- blood pressure and breathing rate drop
- deepest sleep occurs





## NREM Stage 2

- body temperature drops and heart rate begins to slow
- brain begins to produce sleep spin
- lasts approximately 20 minutes

## REM Sleep

- brain becomes more active
- body becomes relaxed and immobilized
- dreams occur
- eyes move rapidly

# Consciousness

## Awake

### Alert
- **Beta** waves

**B**usting out work

### Tired
- **Alpha** waves

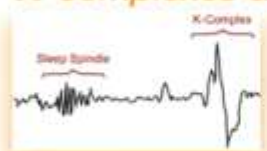
**A**bout to fall asleep

## Asleep

### NON-REM

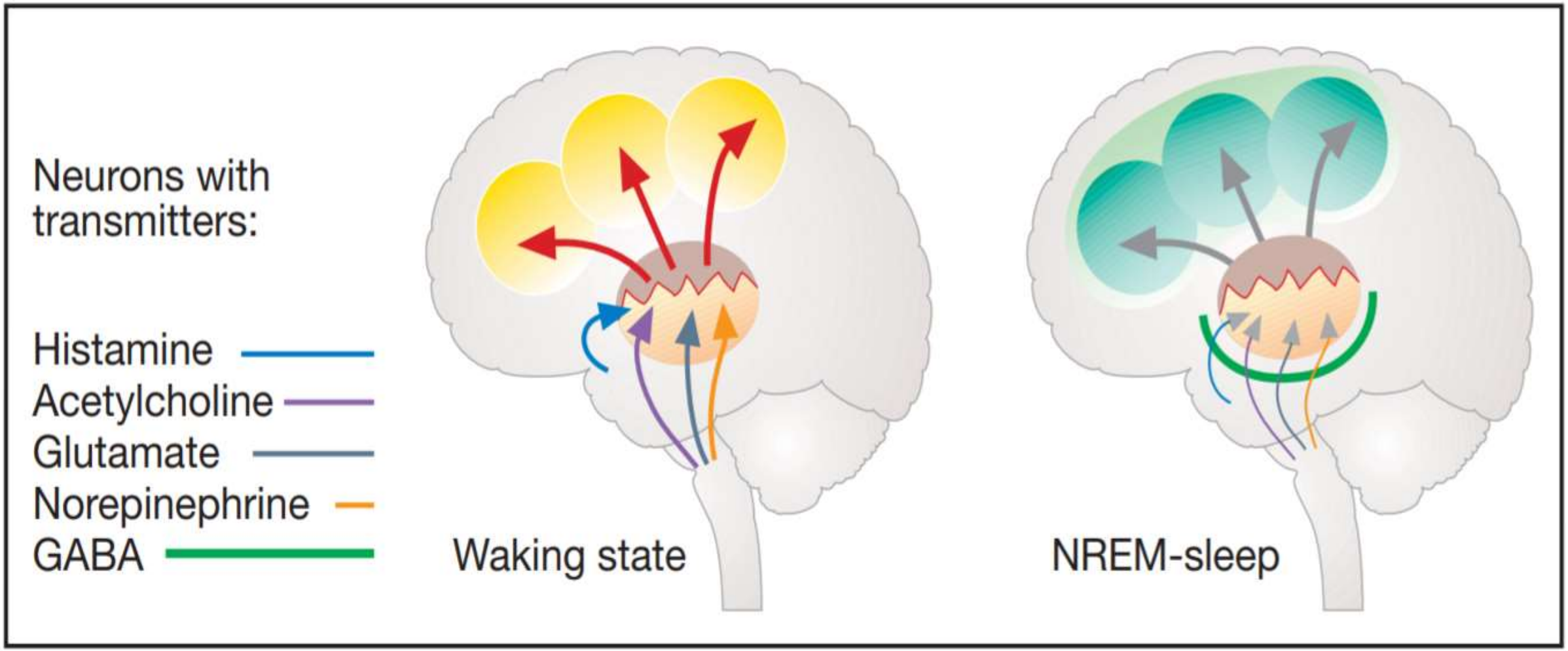
#### N1
- **Theta** waves

#### N2
- **K**-complexes & sleep spindles

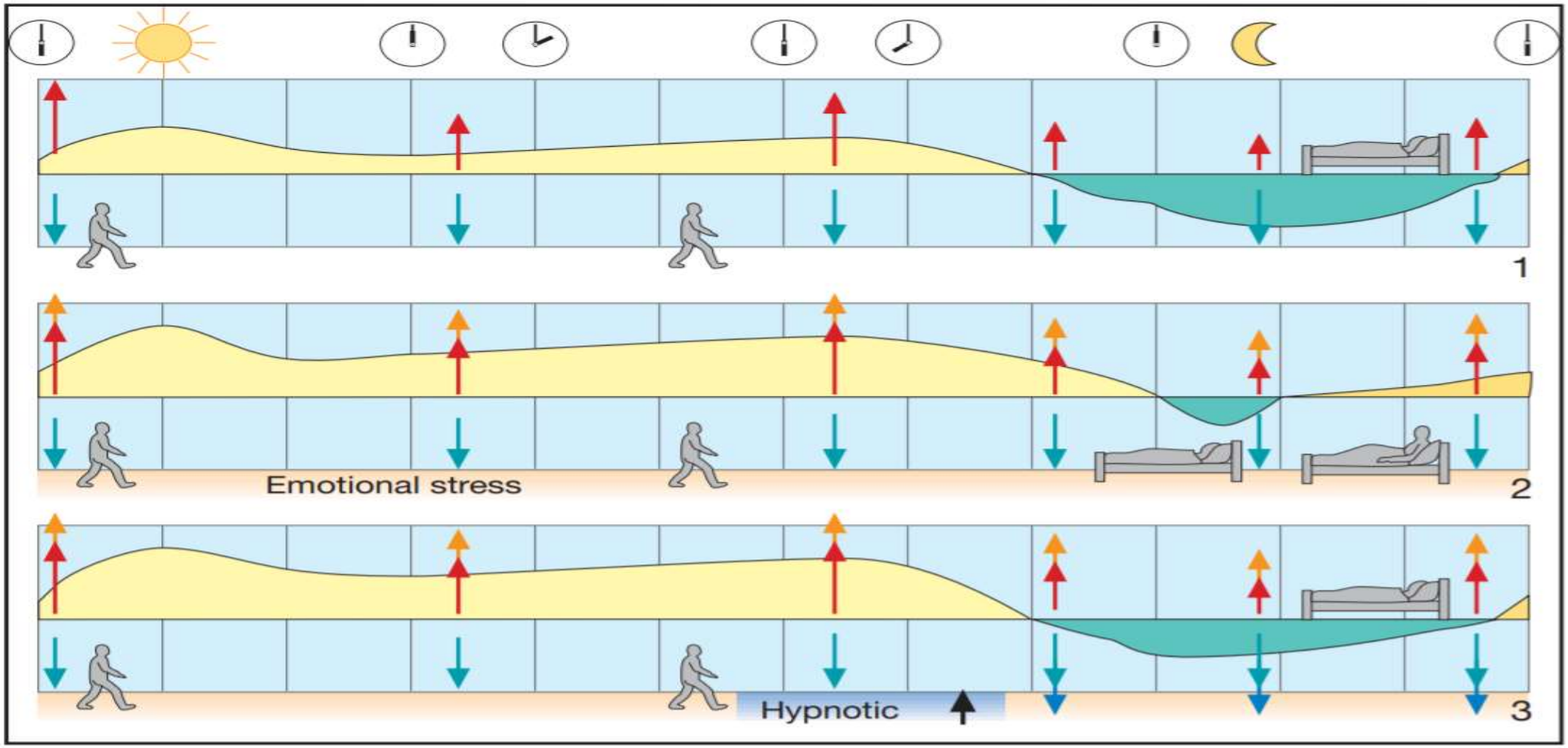



#### N3
- **Delta** waves

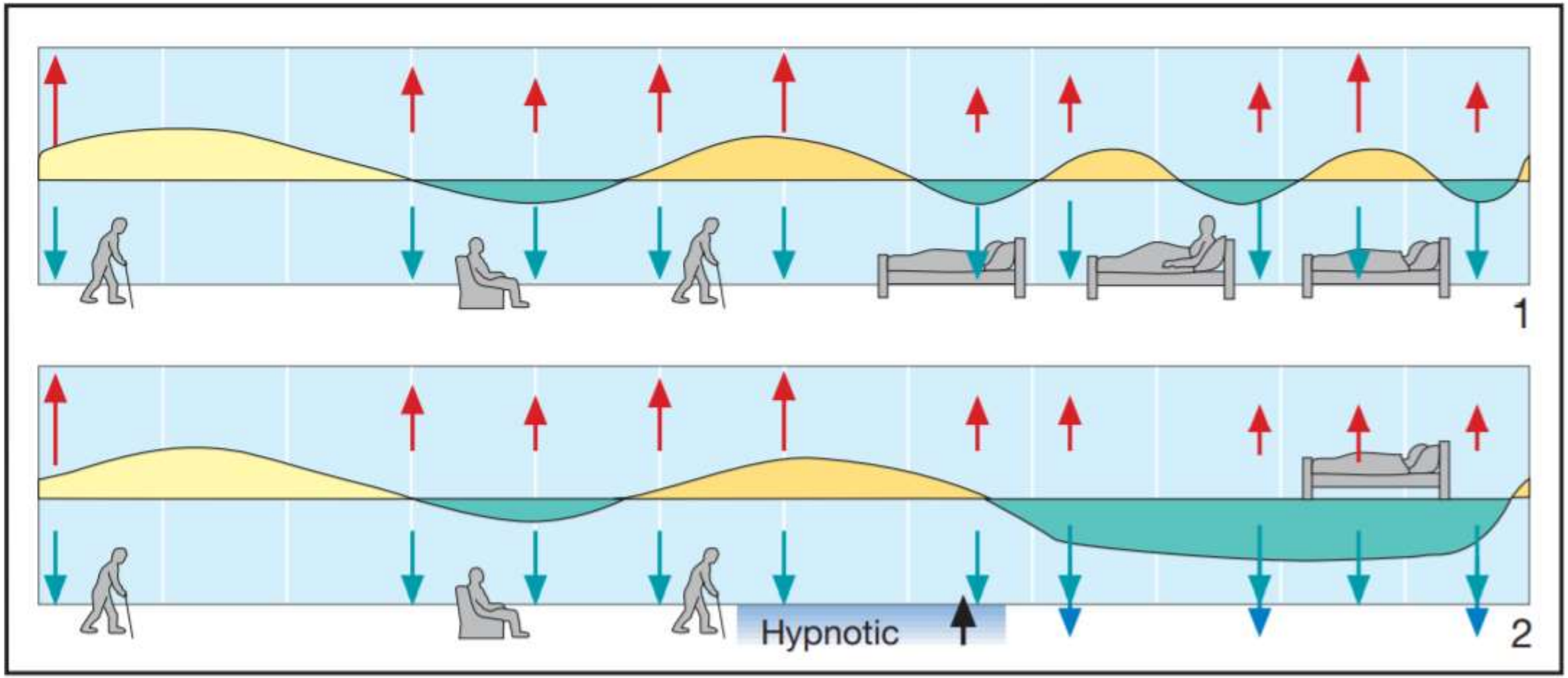
### REM
- **Beta** waves




**A. Transmitters: waking state and sleep**




**B. Wake-sleep pattern, stress, and hypnotic drug action**




**C. Changes of the arousal reaction in the elderly**

## CLASSIFICATION

### 1. *Barbiturates*

| *Long acting* | *Short acting* | *Ultra-short acting* |
|---|---|---|
| Phenobarbitone | Butobarbitone | Thiopentone |
| | Pentobarbitone | Methohexitone |

### 2. *Benzodiazepines*

| *Hypnotic* | *Antianxiety* | *Anticonvulsant* |
|---|---|---|
| Diazepam | Diazepam | Diazepam |
| Flurazepam | Chlordiazepoxide | Lorazepam |
| Nitrazepam | Oxazepam | Clonazepam |
| Alprazolam | Lorazepam | Clobazam |
| Temazepam | Alprazolam | |
| Triazolam | | |

### 3. *Newer nonbenzodiazepine hypnotics*

Zopiclone, Zolpidem Zaleplon

- CNS Barbiturates produce dose-dependent effects:

  sedation → sleep → anaesthesia → coma.
- Hypnotic dose (100-200 mg of a short acting barbiturate)
- Shortens the time taken to fall asleep & increases sleep duration.
- The sleep is arousable, but confused and unsteady if waken early.
- Night awakenings are reduced.
- REM and stage 3, 4 sleep are decreased;
- REM-NREM sleep cycle is disrupted
- The effects on sleep become progressively less marked if the drug is taken every night consecutively.
- Sedative dose (smaller dose of a longer acting barbiturate)
- Given at daytime can produce drowsiness, reduction in anxiety and excitability.

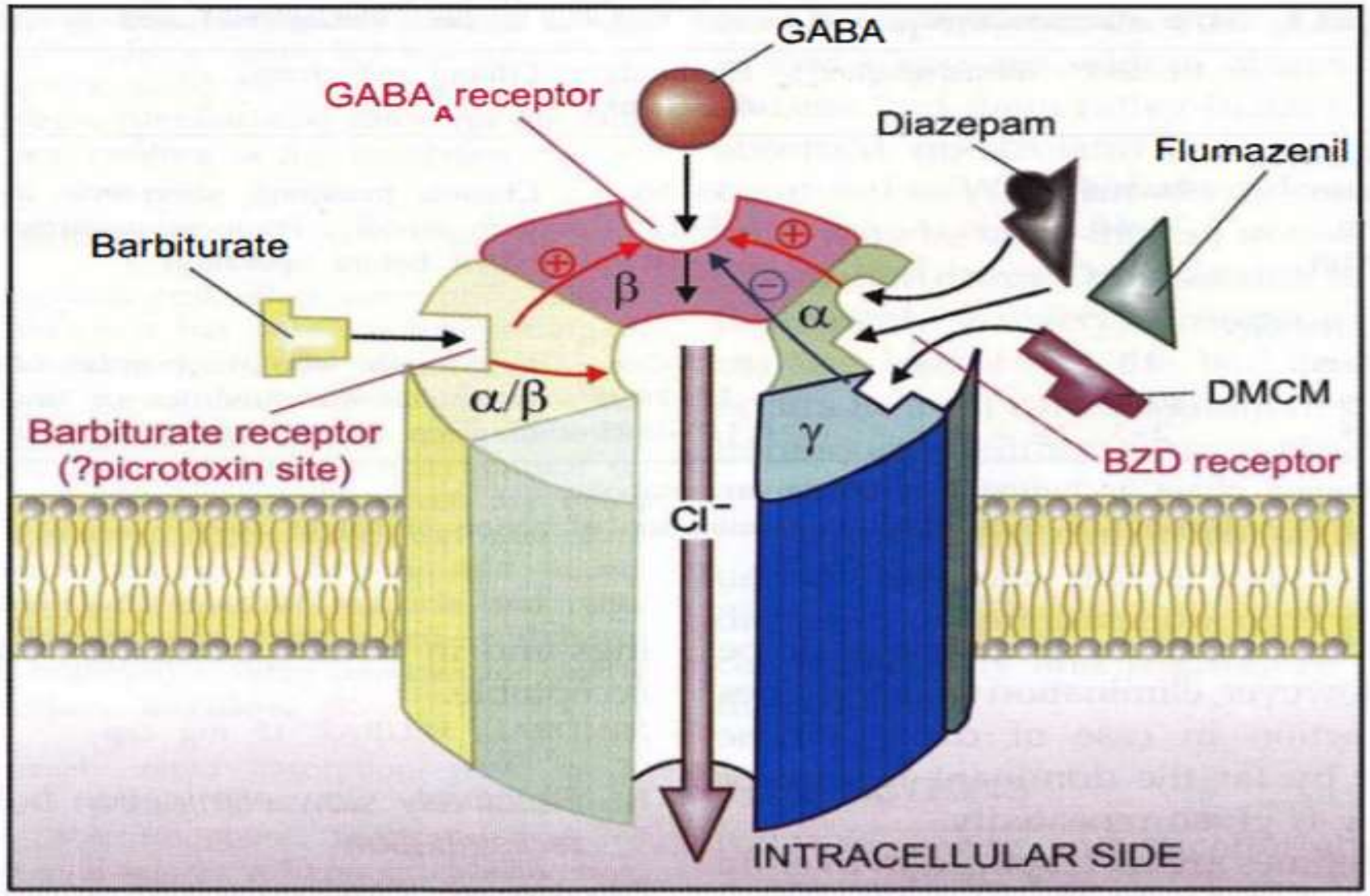



**Fig. 29.3:** Schematic depiction of GABA$_A$-benzodiazepine receptor-chloride channel complex

The chloride channel is gated by the primary ligand GABA acting on GABA$_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates GABA$_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl$^-$ channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl$^-$ channel directly as well. Bicuculline blocks GABA$_A$ receptor, while picrotoxine blocks the Cl$^-$ channel directly

# Mechanism of Action

- Barbiturates appear to act primarily at the GABA : BZD receptor-Cl channel complex
- Potentiate GABAergic inhibition by increasing the lifetime of Cl- channel opening induced by GABA.
- Barbiturates directly increase Cl conductance.

**BARBITURATES** USE: Promote sleep or to calm patients.

Sedation → Sleep → Anaesthesia → Coma.

**RESPIRATION** ↓ higher doses. (Neurogenic, Hypercapneic )

**SKELETAL MUSCLE**: Anaesthetic doses ↓ muscle contraction by depressing excitability of neuromuscular junction.

**SMOOTH MUSCLES:** Tone and motility of bowel ↓ hypnotic doses

**KIDNEY:** ↓ **U**rine flow by ↓ BP and increasing ADH release.

# PHARMACOKINETICS

- Absorbed from the G.I. tract.
- CNS - lipid solubility.
- Plasma protein binding e.g. thiopentone 75%, pentobarbitone 35%,
- Cross placenta and are secreted in milk.
- Redistribution: After i.v. injection, consciousness regained in 6-10 min
- Short acting barbiturate may last just 6-10 hours
- Elimination half life, is 12-40 hours.
- Metabolized in liver by oxidation, dealkylation and conjugation.
- Excretion unchanged in urine

(Alkalinization of urine increases ionization and excretion)

# Adverse reactions

- Intolerance: excitement, lassitude, paroxysmal pain.
- Allergic : Urticaria, angioneurotic edema, thrombocytopenic purpura.
- Megaloblastic anemia
- Depression of fetal respiration
- Hepatic porphyria
- Drug automatism: Confusion and amnesia, a patient may repeatedly take the barbiturate at night and poison himself.
- Tolerance: (i) Increased hepatic inactivation and
  (ii) Adaptation of the neuronal tissue to the drug.
- Drug dependence: Impaired reflexes, hypotonia, nystagmus

# Mechanism of Action

- BENZODIAZEPINES (BDZ): These compounds have largely replaced the barbiturates as hypnotic
- GABA, the most potent inhibitory transmitter in the CNS controls the state of neuronal excitability.
- It acts by binding to the neuronal GABA A receptor and opens the chloride channels.
- Increase the chloride ion concentration in the neuron.
- This causes hyperpolarisation of the neuronal membrane, making it more difficult for the excitatory neurotransmitters to depolarize the cell.

# Pharmacological actions

Benzodiazepines

Anxiolytics

Sedative-Hypnotics

Anticonvulsants

Muscle relaxants

# Absorption, fate and excretion:

- Given orally, diazepam and chlorazepate : Small intestine;
- The only BDZ : IM site are lorazepam and midazolam.
- Rectal route for diazepam is generally used in the convulsing patient.
- The duration of action following a single dose dependent
- Metabolized by hepatic microsomal CYP3A4 and 2C19 enzymes,
- The t½ is prolonged over 60 years age and infants due to reduced hepatic clearance

# Adverse reactions

- Depression of CNS: drowsiness, lethargy and ataxia.
- Impairment of visual-motor coordination, behavioural changes, daytime sedation, and anterograde amnesia.
- Leucopenia, allergy, photosensitisation, vertigo, headache, impaired sexual function and menstrual irregularities.
- Patients develop tolerance to the sedative
- Withdrawal syndrome
- Administration of BDZ to the mother before delivery can cause apnoeic spells, reluctance to feed, hypotonia and hypothermia in the newborn **(floppy baby syndrome).**
- Drug interactions: CNS depressants such as alcohol, barbiturates and amitriptyline.

# NON-BENZODIAZEPINE HYPNOTICS

- Zopiclone
- Cyclopyrrolone hypnotic
- It is an agonist subtype of BZD receptor
- Does not alter REM sleep - Prolong stages 3 and 4.
- Do not disturb sleep architecture or produce hangover or withdrawal phenomena on discontinuation

# BENZODIAZEPINE ANTAGONIST

**FLUMAZENIL**

- It is a BZD analogue which has little intrinsic activity
- Competes with BZD agonists as well as inverse agonists for BZD receptor
- Reverses their depressant or stimulant effects respectively.

Flumazenil abolishes the hypnogenic, psychomotor, cognitive and EEG effects of BZDs.

Flumazenil is absorbed orally

On i.v. injection, starts in seconds and lasts for 1-2 hr;

Elimination half life is 1 hr, due to rapid metabolism

**USE:** To reverse BZD anaesthesia, BZD overdose

- Melatonin acts mainly on two receptors MT1 and MT2 which are found in hypothalamus, hippocampus, cerebellum and other parts of the brain.
- It is involved in sleep-wake cycle and thermoregulation.
- It plays an important role in the circadian timings system (chronobiotic actions).

# Melatonin

- It is N-acetyl-5-methoxy tryptamine, the principal hormone of the pineal gland
- Synchronizing sleep-wakefulness cycle with the circadian rhythm.
- High doses (80 mg) of melatonin can induce sleep,
- Low doses (2-10 mg) do not depress the CNS, falling asleep.
- Ramelteon
- It is a melatonin receptor agonist
- Novel hypnotic for sleep onset insomnia

# Cognitive enhancers

- Cognitive enhancers are drugs that can improve cognitive performance. Some examples of cognitive enhancers include:
- **Modafinil**: A eugeroic drug that promotes wakefulness and alertness. It was originally used to treat narcolepsy, obstructive sleep apnea, and shift work sleep disorder.
- **Methylphenidate**: A dopamine and noradrenaline reuptake inhibitor. It's sold under the brand names Ritalin and Concerta.
- **D-amphetamine**: A dopamine and noradrenaline reuptake inhibitor. It's sold under the brand name Adderall.
- **Caffeine**: A non-selective adenosine receptor antagonist.
- **Nicotine**: A nicotinic cholinergic receptor agonist

# Acknowledgement


- The Presentation is being used for educational and non commercial Purposes
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