

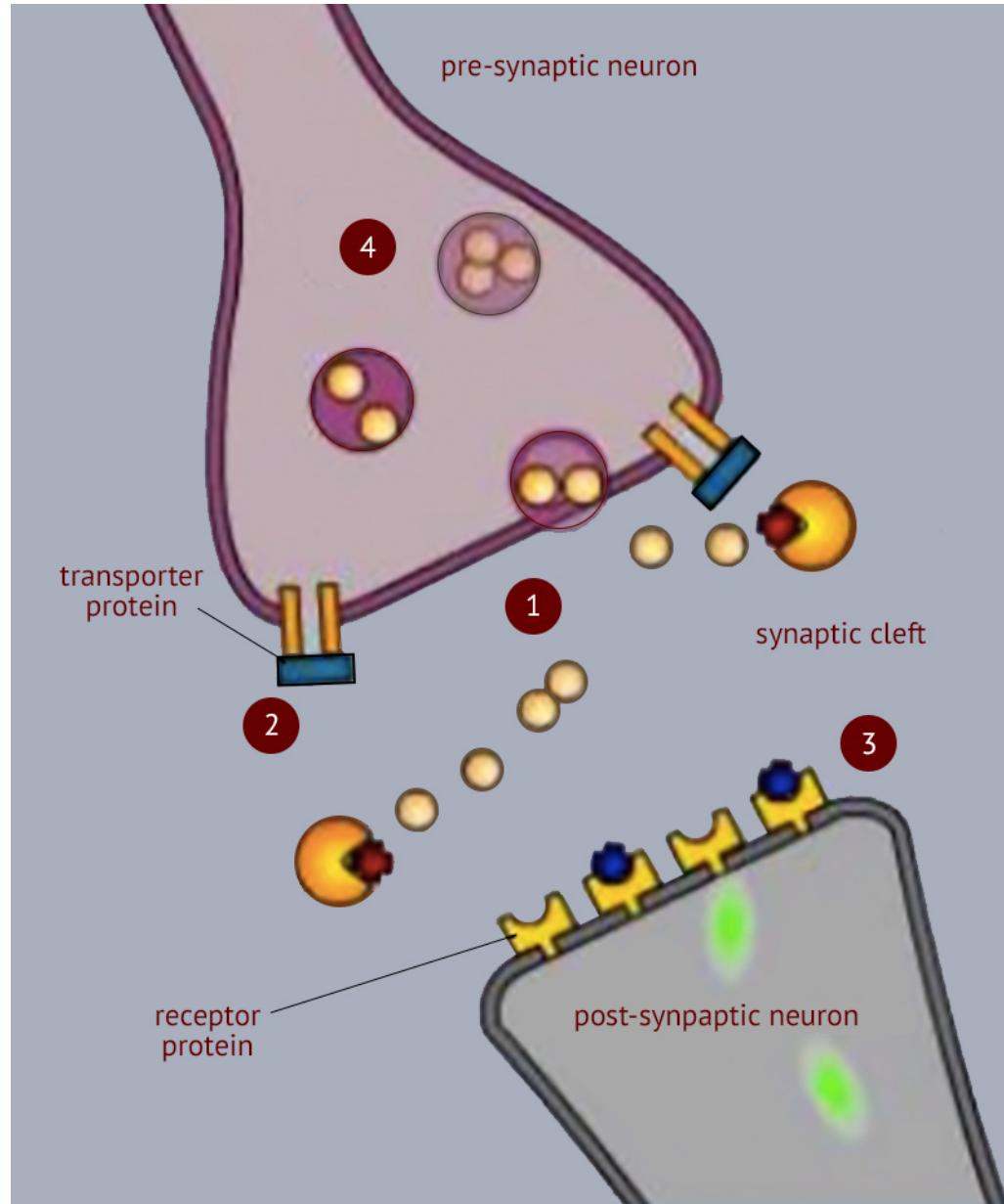
PHARMACOLOGY OF CNS STIMULANTS

PHA 425

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INTRODUCTION

- Psychotropic (also called psychoactive) agents are drugs that affect mood and behaviour.
- They influence the state of the mind and mental processes.
- Some of these agents can be used to manage CNS disorders.
- They are also important because they are substances that have abuse potential.



CLASSIFICATION

- They can be classified as follows:
 - (1) CNS stimulants
 - (2) Sedative-hypnotics
 - (3) Antipsychotics
 - (4) Antidepressants e.t.c.



CNS DEPRESSANTS

- They slow down normal brain function.
- In higher doses, some can become general anaesthetics.
- Tranquillizers and sedatives are examples of CNS depressants.
- They can be divided into two groups, based on their chemistry and pharmacology:

Barbiturates (e.g. thiopental)

Benzodiazepines (e.g. diazepam)

CNS DEPRESSANTS CONTD

- There are many CNS depressants, and most act on the brain similarly they affect the neurotransmitter gamma-aminobutyric acid (GABA).
- GABA works by decreasing brain activity (**Inhibitory Postsynaptic Potential-IPSP**).
- Although different classes of CNS depressants work in unique ways, ultimately it is their ability to increase GABA activity that produces a drowsy or calming effect.

CNS STIMULANTS

- These are agents that increase the excitation of the CNS e.g.
 - (1) Respiratory stimulants,
 - (2) Convulsants and
 - (3) Psychomotor stimulants.
- NB: These agents cannot reverse the effect of pharmacologically induced CNS depression.
- Examples of reversal agents are flumazenil and naloxone

RESPIRATORY STIMULANTS

Examples are:

Doxapram

Prethcamide

Mechanism of Action

They excite the respiratory centre in the medulla to increase the depth of breathing and rate of respiration. They can be used to counteract post-anaesthetic respiratory depression and to aid chronic obstructive pulmonary disease (COPD).

RESPIRATORY STIMULANTS CONTD

Adverse Effects

- Restlessness
- Tachycardia
- Convulsion at higher doses.

CONVULSANTS

Examples are:

- Picrotoxin
- Strychnine
- Bicuculline
- Pentylenetetrazole (PTZ) or Leptazol/metrazol

NB: They are only used as experimental tools to evaluate the anticonvulsant potential of drugs and **not for clinical use.**

CONVULSANTS CONTD

- Strychnine is a plant alkaloid
- It acts more as a spinal cord stimulant.

Mechanism of action:

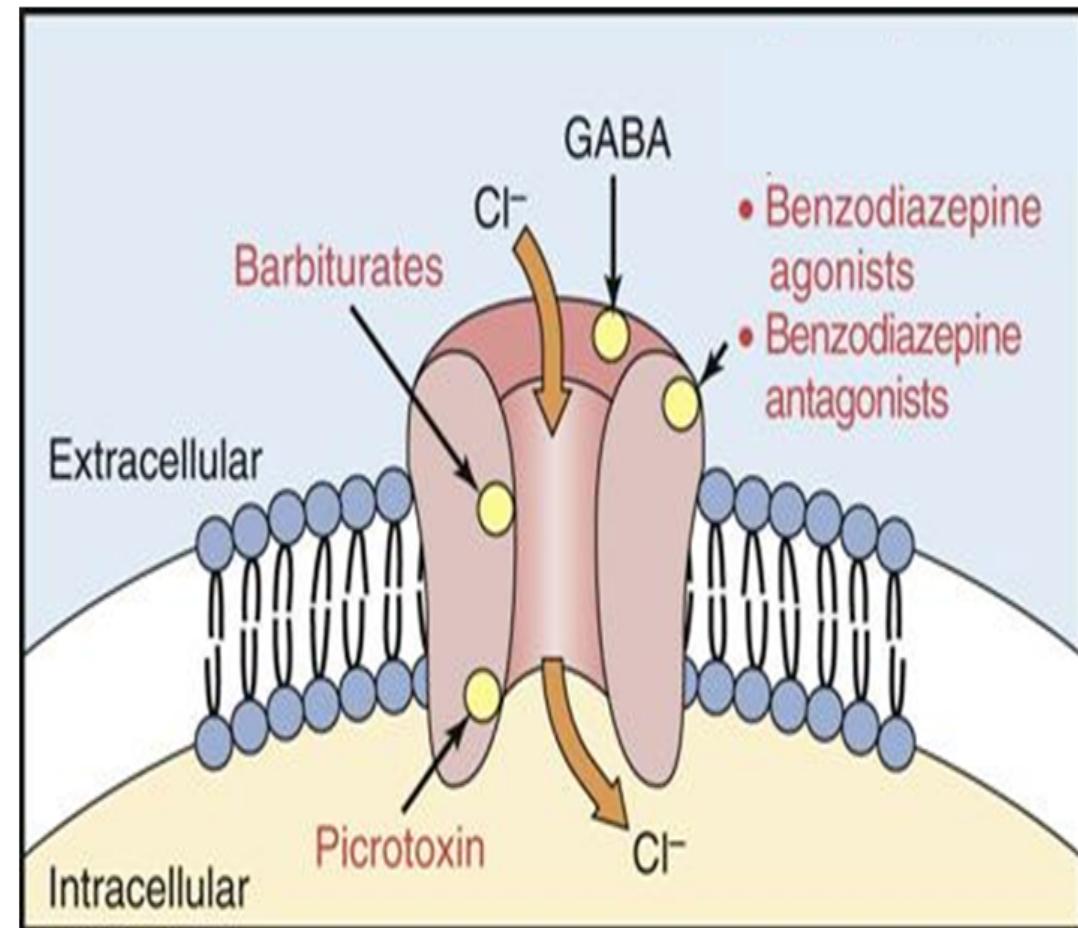
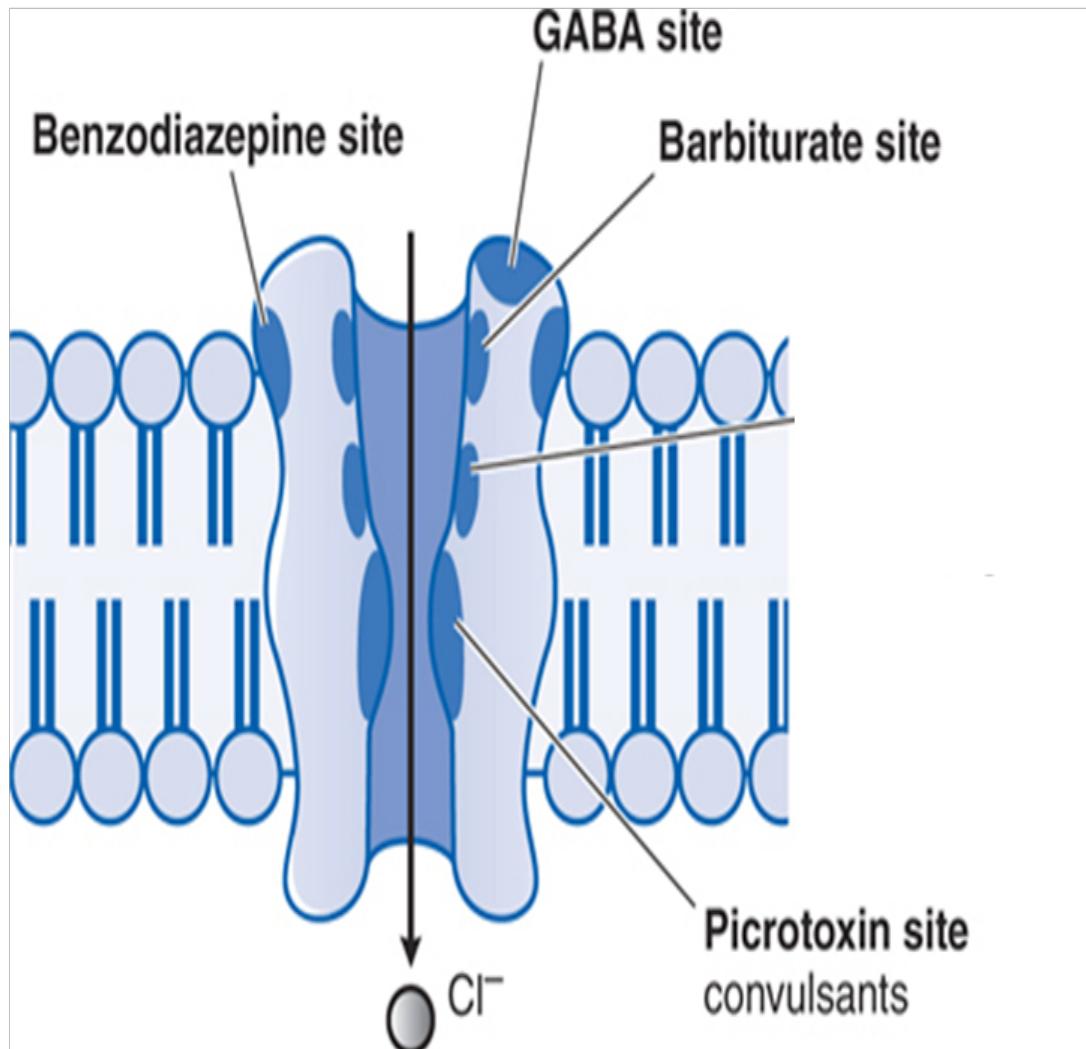
It acts by blocking glycine receptors (inhibitory mechanism) thereby allowing excitatory impulses to be greatly exaggerated.

NB: I.V. Diazepam or clonazepam can be used to treat strychnine poisoning.

CONVULSANTS CONTD

- Picrotoxin is obtained from the seeds of *Anamirta cocculus*-fish berries
- Picrotoxin blocks the Cl- ion channel of GABA_A receptor.
- Bicuculline, also a plant alkaloid, causes convulsion by antagonising GABA_A receptors.
- PTZ directly depolarises CNS neurons and also antagonises Cl- ion conductance of GABA_A receptors.

NB: Benzodiazepines e.g. Diazepam, Clonazepam are drugs of choice in case of poisoning.



PSYCHOMOTOR STIMULANTS

- **Examples include:**
 - (i) Amphetamine and its derivatives e.g.
- Dexamphetamine
- Methamphetamine,
- Methyleneoxymethamphetamine (MDMA-ecstacy)
- Methylphenidate
- Dexfenfluramine
- Fenfluramine
- Sibutramine.

PSYCHOMOTOR STIMULANTS CONTD

(ii) Non-amphetamines e.g. pemoline, modafinil.

(iii) Methylxanthines e.g.

- Caffeine
- Theophylline and derivatives (aminophylline, etophylline)
- Theobromine.

(iv) cocaine

PSYCHOMOTOR STIMULANTS CONTD

Pharmacological effects:

These agents have notable influence on

- mental function
- behaviour (to produce excitement and euphoria)
- increased motor activity
- reduction in fatigue.

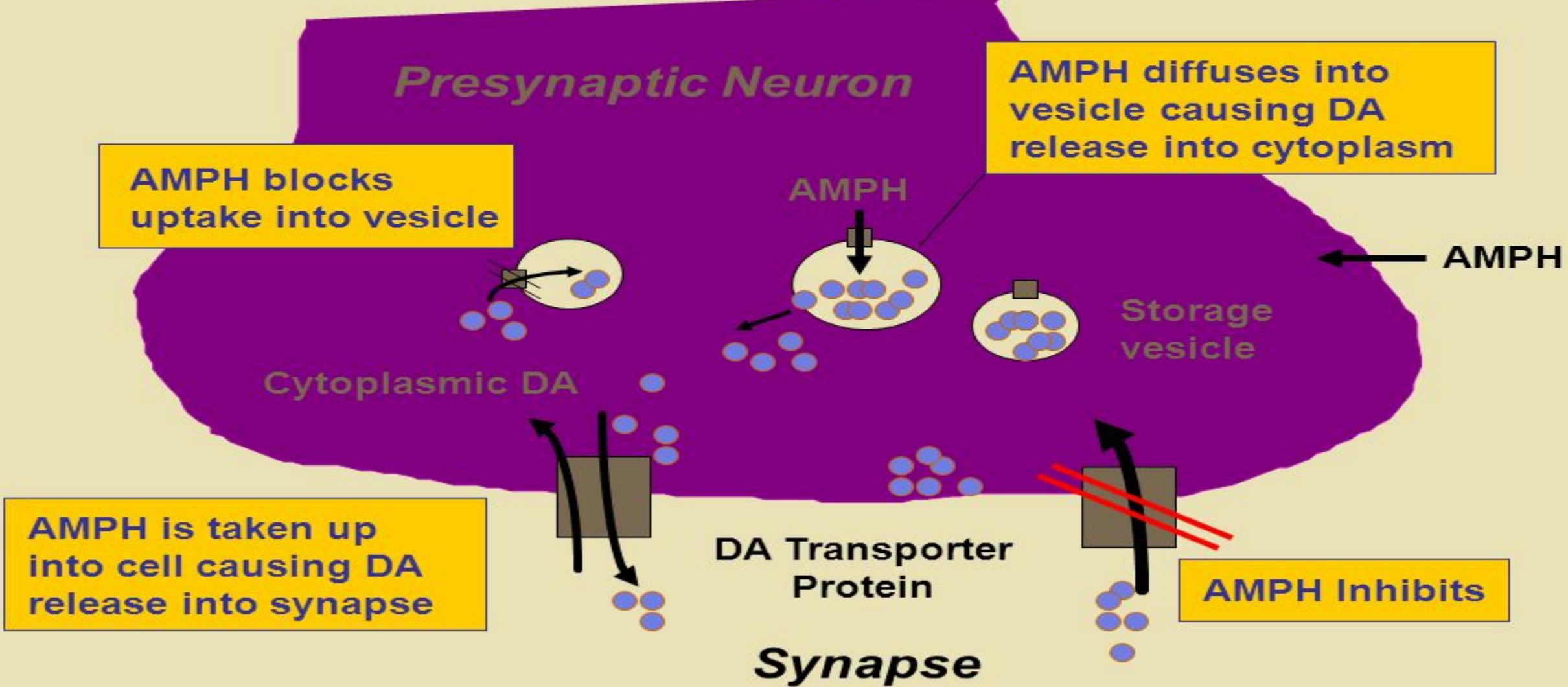
AMPHETHAMINE AND DERIVATIVES

Mechanism of action:

They displace dopamine and norepinephrine from storage vesicles in CNS neurones thereby releasing them into the synapses.

The Mechanisms of Action of Amphetamine

Wilens and Spencer. *Handbook of Substance Abuse: Neurobehavioral Pharmacology*. 1998;501-513.



AMPHETHAMINE AND DERIVATIVES

CONTD

Pharmacological effects:

- They promote wakefulness and alertness,
- Reduced fatigue,
- Euphoria,
- Anorexia,
- Stereotyped and psychotic behaviour,
- Increased sympathetic activity leading to increased blood pressure and decreased GIT motility

AMPHETHAMINE AND DERIVATIVES

CONTD

- **Pharmacokinetics:**
- lipophilic,
- it crosses the BBB,
- well absorbed orally.

AMPHETHAMINE AND DERIVATIVES CONTD

- Clinical uses:
- Attention Deficit Hyperactive Disorder (ADHD) especially in children i.e. methylphenidate, pemoline.
- Narcolepsy- methylphenidate, modafinil (non-amphetamine), MAO-B (selegiline) is also useful in managing narcolepsy by making dopamine more available at the synapse.
- Obesity – fenfluramine and dexfenfluramine were used to manage obesity but due to tolerance and potential for dependence their use has been discouraged. However sibutramine (a new drug) is now in use for obesity.

AMPHETHAMINE AND DERIVATIVES

CONTD

- **Adverse effects:**

- (1) Tolerance (especially the anorexic effects)
- (2) dependence (more of psychological dependence)
- (3) euphoria
- (4) Dizziness
- (5) Tremors

AMPHETAMINE AND DERIVATIVES

CONTD

- (6) Hypertension
- (7) irritability
- (8) anorexia
- (9) Insomnia
- (10) convulsions and psychotic manifestations could occur at higher doses.

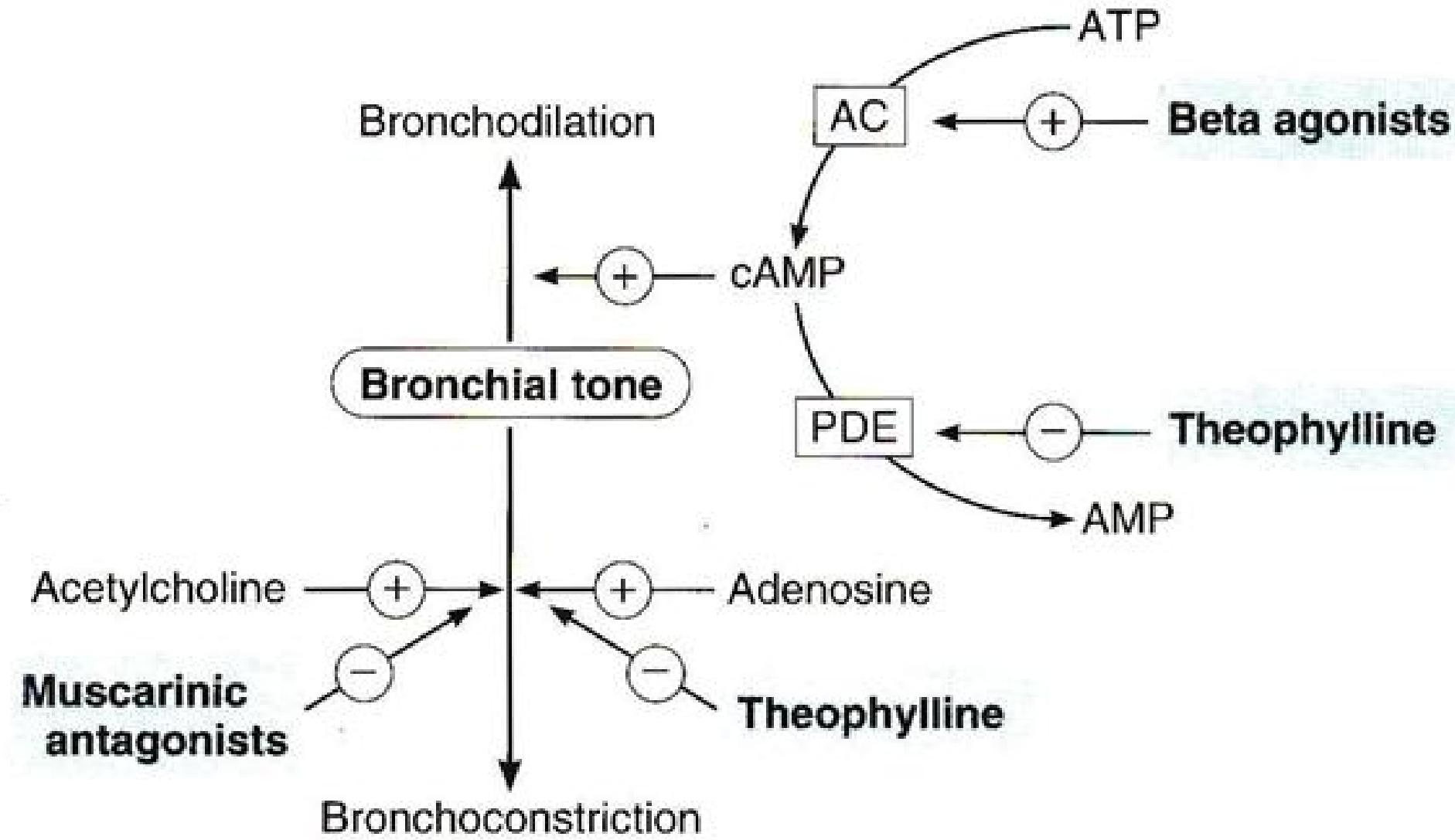
AMPHETHAMINE AND DERIVATIVES

CONTD

- Amphetamine toxicity can be managed using I.V. diazepam, haloperidol (for agitation and psychotic symptoms),
- gastric lavage, acidification of urine to facilitate its excretion being a basic drug.
- Antihypertensives can be used to control hypertension as a result of increased sympathetic activity.
- Sudden death can occur with MDMA.

METHYLXANTHINES

- Caffeine is found in highest concentration in coffee. It is also present in tea and kola. Some energy drinks have high caffeine concentration. Theophylline is found in tea while theobromine is from cocoa.
- Mechanism of action: it is believed that they increase the levels of cAMP (3,5- cAMP) by inhibiting the phosphodiesterase enzyme (leading to bronchodilatation/vasodilatation).



AC- Adenyl cyclase; PDE- Phosphodiesterase

METHYLXANTHINES CONTD

- It is also believed that they function by antagonising adenosine at the cell surface adenosine receptors (A₁, A₂& A₃).
- NB: adenosine exerts inhibitory effects leading to drowsiness, motor incoordination, CNS depression, anticonvulsant action and bronchoconstriction.

PHARMACOLOGICAL ACTIONS

- CNS stimulation: caffeine > theophylline > theobromine.
- This results into wakefulness, alertness and increased capacity to do intellectual work. Reduction of fatigue, no euphoria, stereotyped behaviour or psychotic manifestations.
- CVS: they increase heart rate, increase cardiac output and decrease oxygen tension in the brain.

PHARMACOLOGICAL ACTIONS

CONTD

- Kidney: acts as mild diuretic
- Bronchial smooth muscle relaxation
- Increased gastric acid and pepsin secretion
- Theophylline inhibits the release of histamine and other mediators in the mast cells which contributes to its therapeutic benefits in bronchial asthma.

CLINICAL USES

- Caffeine can be combined with aspirin for the treatment of ordinary headache, and with ergot alkaloids for migraine.
- Asthma and chronic obstructive pulmonary disease

ADVERSE EFFECTS

- Dyspepsia,
- insomnia,
- restlessness,
- vomiting,
- palpitations.

Question:

- Does caffeine cause habituation or dependence?