Drugs acting on Respiratory System:

Regulation of respiration :

I- Nervous regulation:

1- **Respiratory center in medulla:** affected by impulses from cerebral cortex, hypothalamus, lungs or circulatory system.

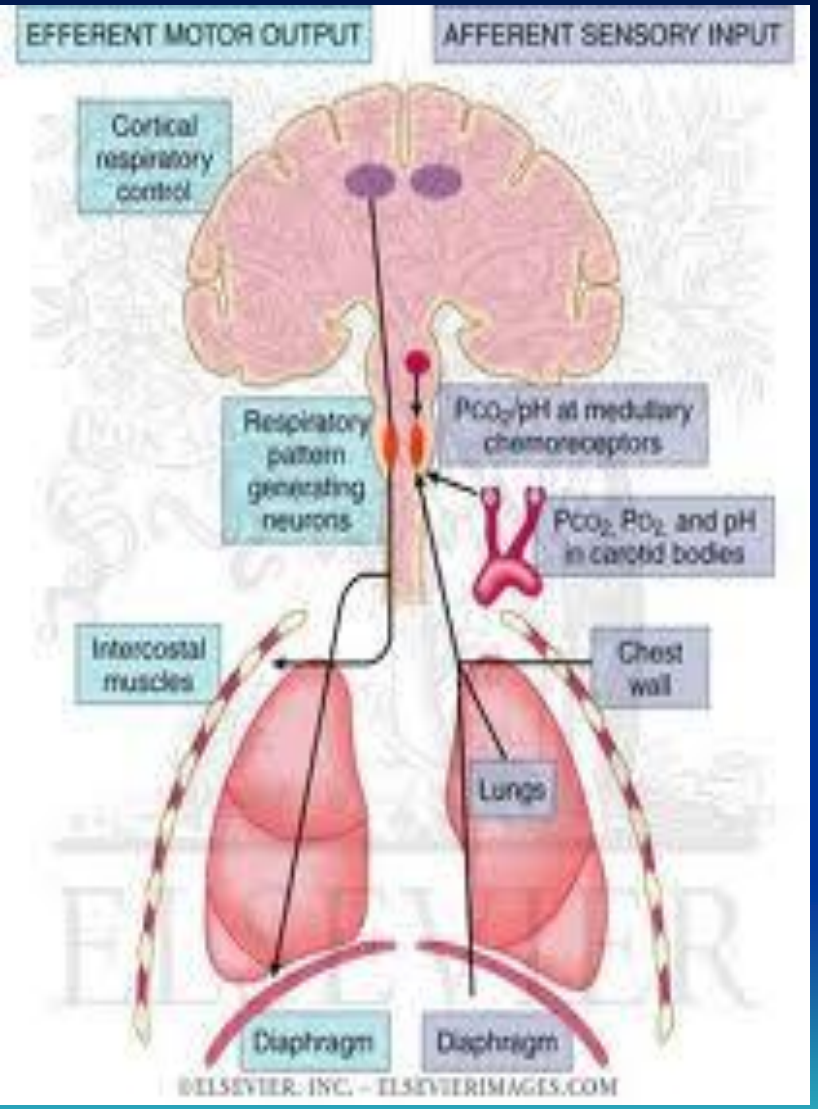
II- Chemical regulation:

Respiration is regulated by some chemical factors:

1- P CO_2: CO_2 tension (acting on medullary chemoreceptors).

2- P O_2: O_2 tension (acting on chemoreceptors in the aortic and carotid bodies).

3- pH of the blood.


EFFERENT MOTOR OUTPUT
AFFERENT SENSORY INPUT
Cortical respiratory control
Respiratory pattern generating neurons
PCO_2/pH at medullary chemoreceptors
PCO_2, PO_2, and pH in carotid bodies
Intercostal muscles
Chest wall
Lungs
Diaphragm
Diaphragm
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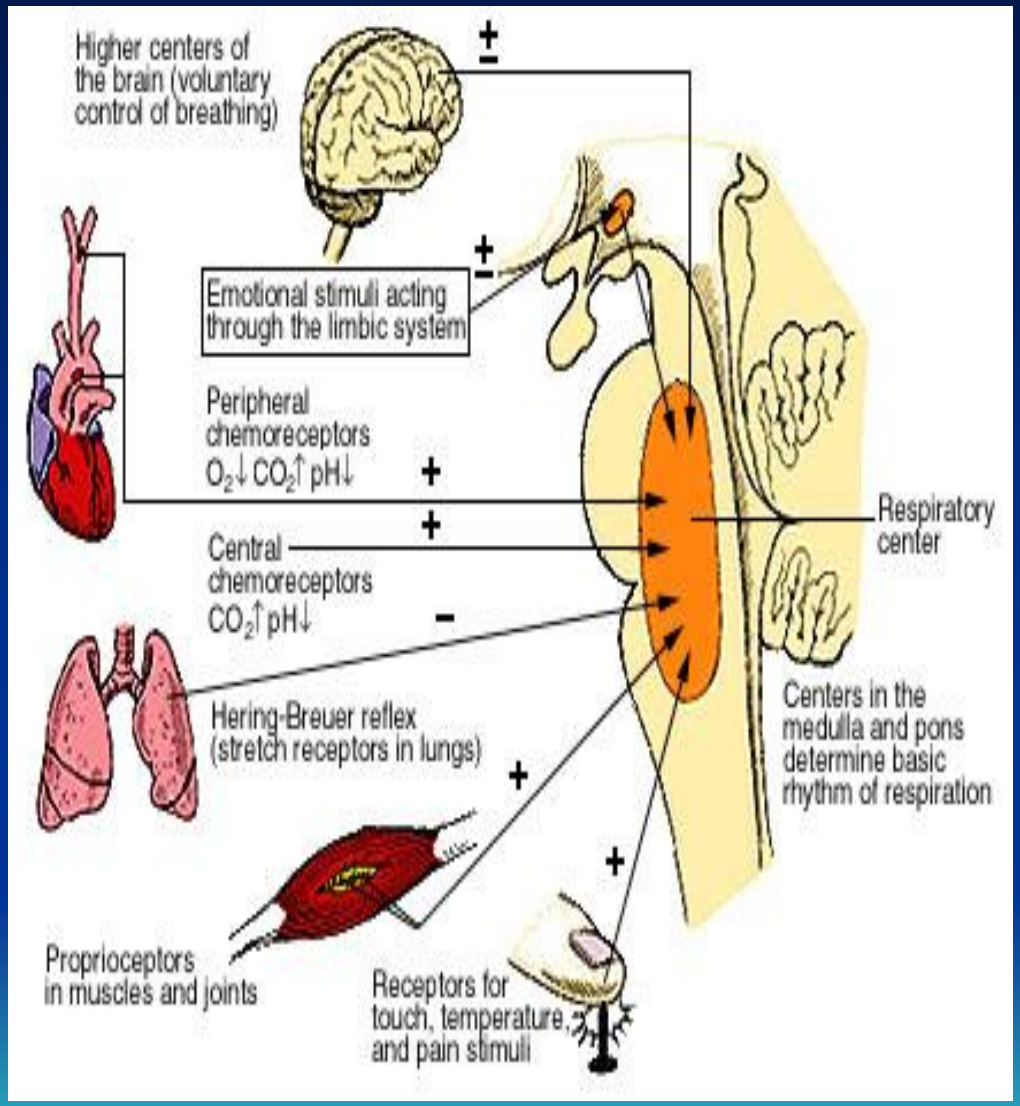

Higher centers of the brain (voluntary control of breathing)
Emotional stimuli acting through the limbic system
Peripheral chemoreceptors
$O_2\downarrow$ $CO_2\uparrow$ pH↓
Central chemoreceptors
$CO_2\uparrow$ pH↓
Respiratory center
Hering-Breuer reflex (stretch receptors in lungs)
Centers in the medulla and pons determine basic rhythm of respiration
Proprioceptors in muscles and joints
Receptors for touch, temperature, and pain stimuli

Respiratory defense mechanism :

For protecting the respiratory tract from injury or infection

1- Sneezing 2- Coughing.

3- Increased mucous production in the nose and respiratory tract.

4- Constriction of bronchioles.

5- Mucocilliary apparatus: which facilitate the removal of infective materials.

It consists of mucous and ciliated cells in the respiratory tract.

Drugs acting on Respiratory System:

They include the following:

I-Drugs acting on respiration:

1- Respiratory stimulants.

2- Respiratory depressants.

II- Drugs acting on bronchi:

1- Expectorants.

2- Mucolytics

I- Drugs on respiration:

A- Respiratory stimulants:

Def: These are drugs which increase or quicken or deepen respiration by stimulating respiratory center.

Classification:

1- Direct stimulants of respiratory center:

Mechanism of action:

They stimulate the respiration by stimulating the respiratory center directly.

a- Medullary stimulants (Analeptics):

Picrotoxin, Leptazole, Nikethamide, Doxapram

b- Cerebral cortex stimulants:

- Methylxanthines (Caffeine), atropine, hyoscine, ephedrine and amphetamine.

c- Carbon dioxide (CO_2):

- CO_2 (present normally in air in a concentration of 0.05% but, when in higher concentration not more than 10% → will stimulate respiration).

- CO_2 (present in a concentration more than 10% → will depress respiration).

- CO_2 introduced mixed with O_2 as carbogen-

2- Indirect (Reflex) stimulants of respiratory stimulants-

a- Stimulants of chemoreceptors in the carotid body and aortic arch:

i-High CO_2 ii- Low O_2. iii- pH (acidity).

b- Stimulants of barorecebtors in the aortic arch and carotid sinus:

Changes in blood pressure (Hypotension).

c- Irritants of the skin and mucous membranes:

i- Ammonia inhalation

ii- Alcohol

iii- Camphor (S.C injection).

Mechanism of action:

They act by mild irritation of sensory nerve endings of the skin or mucous membrane of the nose or stomach → reflex stimulation of medullary center including respiratory center → increased respiration

B- Respiratory depressants:

i- Depressants of the respiratory center in the medulla:

Morphine and Diamorphine

ii- Depressants of the sensitivity of respiratory center to CO_2:

Barbiturates and benzodiazepine.

iii- Depressants of cough center (antitussive):

a- Codeine.

b- Dextromethorphan

Cough and anti-tussive drugs:

Cough:

Sudden expulsive expiration of air from respiratory tract and expelled air contains mucous or foreign bodies which may be found in the lung.

Cough center:

It is a cluster of neurons located next to the respiratory center in the medullary area of the brainstem.

Cough (irritant) receptors:

1- These are located throughout the respiratory tract from the pharynx to the smaller air passage in the lung.

2- Stimulation of these receptors→ sends impulses to → cough center in the medulla →cough reflex → causing contraction of respiratory muscles → produce a sharp, forceful expiration.

Types of cough:

1- Productive cough (moist cough):

This type of cough is characterized by production of mucous and inflammatory products.

2- Non- Productive cough (Dry cough):

- This type of cough is characterized by absence of mucous.
- It may occur in the early stages of infection or inflammation when the mucous glands in the respiratory tract have not yet increased production of mucous.

- It may be associated with chronic inflammation (e.g. chronic bronchitis) → where the mucous produced becomes dry and sticky → accumulating in the bronchi or the mucous glands becomes unable to produce mucus.

Anti-tussive drugs (Cough depressants or suppressants):

These are drugs which suppress the coughing that normally remove mucous, cellular debris, exudates and other products in the bronchi due to infections or inflammation.

NB:

a- It is important to avoid large dose in animals with a very productive cough because suppression of coughing with anti-tussive drugs → can result in → accumulation of excessive mucous and debris.

b- Cough suppressants should not be used in animals with chronic bronchitis because coughing prevents obstruction of small air ways by sticky mucous.

I- Centrally acting anti-tussive drugs:

It is the only type used in veterinary medicine because the veterinary patients are unwilling to hold in their mouth long enough to be effective.

Mechanism of action:

They act by direct suppression of coughing center in the medulla. Also, these drugs are opoids so, a part of the effect may be result from their actions on higher centers as tranquilizers.

Butorphanol:

1- It has more potent analgesic activity than morphine.

2- It is used in chronic non-productive cough associated with tracheobronchitis, tracheitis, tonsillitis, pharyngitis and laryngitis originating from inflammatory conditions of upper respiratory.

3- It is used in horses as anti-tussive drug by i.m injection.

4- In dogs: butorphanol given s.c. **(**it is 4 times more potent than morphine, 10 times more potent than pentazocine and 100 times more potent than codeine as antitussive**)**. Orally butorphanol is approximately 15 to 20 times more active than either codeine or dextromethorphan.

5- Butorphanol is a narcotic agonist-antagonist analgesic with potent antitussive activity.

Hydrocodone:

1- Hydrocodone is an effective semisynthetic opioid anti-tussive and analgesic.

2- As an opiate it is also an effective analgesic for mild to moderate pain control

3- Is chemically and pharmacologically similar to codeine but more potent.

4- Five mg of hydrocodone is equivalent to 30 mg of codeine when administered orally.

4- It is combined with an anticholinergic drug (homatropine) to discourage **abuse** by people.

5- The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center.

6- In excessive doses, hydrocodone, like other opium derivatives, will depress respiration.

7- The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant.

8- Hydrocodone can produce miosis, euphoria, physical and psychological dependence.

9- It can be prescribed for small animals but should be used with caution in cats.

Codeine:

1- is methyl morphine; methylation of morphine significantly improves the oral bioavailability by reducing the first-pass effect.

2- Codeine phosphate and codeine sulfate are found in many preparations, including tablets, liquids, and syrups.

3- Codeine has analgesic effects that are about one-tenth that of morphine, but its antitussive potency is about equal to that of morphine.

4- The side effects of codeine are significantly less than those seen with morphine at antitussive doses.

5- Toxicity (especially in cats) is exhibited as excitement, muscular spasms, convulsions, respiratory depression, sedation, and constipation.

Dextromethorphan:

1- It is a synthetic derivative of morphine but, it is technically not considered an opiate because it does not bind to traditional opiate receptors and is not addictive or analgesic.

2- It is the d-isomer of levorphanol (the l-isomer of levorphanol has addictive and analgesic properties).

3- Dextromethorphan is the safest antitussive to use in cats .

Morphine:

1- It is an effective antitussive at doses lower than the doses that produce analgesia and sedation.

2- It is not commonly used for antitussive activity due to side effects and the potential for abuse and addiction.

3- Morphine has poor oral bioavailability due to a significant first-pass effect by the liver.

II- Peripherally acting antit-ussive drugs:

1- They reduce coughing by soothing the mucosal irritation that is initiating the cough.

2- It is not suitable for veterinary patients.

Mechanism of action:

Peripherally acting antitussives may act on either the afferent or the efferent side of the cough reflex.

On the afferent side:

An antitussive may ↓ the input of stimuli by acting as **a mild analgesic or anesthetic on the respiratory mucosa by:**

a- Modifying the output and viscosity of the respiratory tract fluid.

b- Relaxing the smooth muscle of the bronchi in the presence of bronchospasm.

On the efferent side:

An antitussive may make secretions easier to cough up by:

a-increasing the efficiency of the cough mechanism.

Peripherally acting agents are grouped as:

a- Demulcents. **b- Local anesthetics.**

c- Humidifying aerosols and steam inhalations.

Demulcents:

1-They are useful for coughs originating above the larynx.

2- They form a protective coating over the irritated pharyngeal mucosa.

3- They are usually given as syrups or lozenges and include acacia, licorice, glycerin, honey, and wild cherry syrups.

Local anesthetics:

Examples: lidocaine, Benzocaine, Hexylcaine hydrochloride, and Tetracaine).

They are used to inhibit the cough reflex under special circumstances **(e. g. → before bronchoscopy or bronchography)**.

Humidifying aerosols and steam inhalations:

1- They exert an antitussive effect by acting as a demulcent and by decreasing the viscosity of bronchial secretions.

2- Inhaling water as an aerosol or as steam, with or without medicaments (sodium chloride, compound benzoin tincture, eucalyptol), is the most common method of humidification.

II- Drugs acting on bronchi:

1- Expectorants:

Def: These are drugs which increase the volume, fluidity of the bronchial secretions (mucous) and decreasing their viscosity.

Mechanism:

a- They increase the fluidity by generating liquid secretions by respiratory tract cells.

b- They improve the effectiveness of mucocilliary apparatus.

Uses:

They are used with anti-tussive drugs to relieve cough in acute and chronic bronchitis.

Classification of expectorants:

They are classified according to **their route of administration and their site of action into:**

1- Direct (Local) expectorants:

Mechanism of action:

a- They act directly by stimulating the parasympathetic nervous system →↑ the bronchial glands secretion.

b- These drugs are given orally → absorbed → after absorption they are excreted through the bronchial glands → irritating them → ↑ their secretions

They are subdivided into

A- Non inhalant direct (Local) expectorants:

Preparations:

1- Ammonium chloride.

2- Potassium iodide.

3- Sodium iodide.

4- Potassium citrate.

Uses:

They are used only **in chronic not acute bronchitis** due to its irritant effect.

Mechanism of action:

a- These drugs are given orally → absorbed → after absorption they are excreted through the bronchial glands → irritating them → ↑ their secretions.

NB:

Ammonium chloride may ↑ the acidity leading to → sticky mucous.

B- Inhalant direct (Local) expectorants:

Mechanism of action:

1- They are applied by inhalation (these substances are volatiles vaporized with the steam) → the inhaled vapors → directly stimulate the bronchial glands → ↑ the respiratory secretions.

Method of application:

They are volatile oils such as (benzoin, terpin and eucalyptus), best applied by filling a bucket for large animals or bowel for small animals with steaming hot water.

2- Then pouring few drops of inhalant on to the water.

3- The heat vaporizes the inhalant with the steam.

4- The animal will inhale the drug when its head is held in the steam.

Uses:

They are of value in clearing pharyngeal and laryngeal exudates.

Preparations:

a- Benzoin. b-Terpin c- Eucalyptus

2- Indirect (Reflex) expectorants:

Mechanism of action:

They act by being given orally → irritation of the sensory nerve endings in the esophagus and gastric mucosa → reflexly stimulate the vagal center in the medulla → nausea and ↑ in the rate of production and the volume of secretions.

Preparations:

Indirect expectorants of vegetable origin (Emetic expectorants):

1- These are plants containing irritant alkaloids like emetine and cephaline or scillarine which irritate the oral, pharyngeal and gastric mucosa to the extent of causing nausea → ↑ the all body secretions including saliva, sweat and respiratory secretions.

2- They are of value in all type of respiratory inflammation.

3- They are given in sub emetic dose.

4- They are of no value in ruminants.

They include:

1- Ipecacuanha:

- Ipecac contains alkaloids (emetine and cephaline).

- It is used in the form of tincture ipecac.

2- Squil:

- It contains the glycosides scillarin A and B.

- It is used as tincture or syrup squil.

3- Balsam Tolu:

- It is used as a syrup of Tolu for dogs.

Indirect expectorants of inorganic origin:

1- Ammonium salts:

Ammonium carbonate.

Ammonium chloride

- They reduce the pH and viscosity of secretions while, increasing the volume of secretions and improving the activity of mucocilliary apparatus.

- They are indicated in both acute and chronic bronchitis.

2- Antimony potassium tartrate:

It is called tartar emetic

Mucolytics:

- These are drugs which liquefy the viscous secretions of the respiratory tract.

-They are recommended in certain respiratory diseases as pulmonary emphysema.

Preparations:

a- Bromhexine. **b- Bromhexine HCl (Bisolvon).**

c- Acetylcysteine **d- Carbocysteine.**

e- Methylcysteine.

NB: →

- With infection or inflammation, the inflammatory cells move into the infected area to overcome the infectious agent or to remove cellular damage.
- DNA which found in inflammatory cells or cellular debris reacts with mucous to ↑ its viscosity→ making it more sticky forming → polymers of glycoproteins linked together by disulfide bond. So, the cilliary apparatus becomes unable to remove these polymerized mucous.

Mechanism of action:

Mucolytics are given (orally, by inhalation or by instillation) have free sulfhydryl groups that open mucoprotein (polymerized mucous) disulfide bonds, reducing the viscosity of mucus. Therefore, facilitate its removal by the cilliary apparatus.

Uses:

1- As mucolytic agent.

2- Chronic bronchitis in dogs.

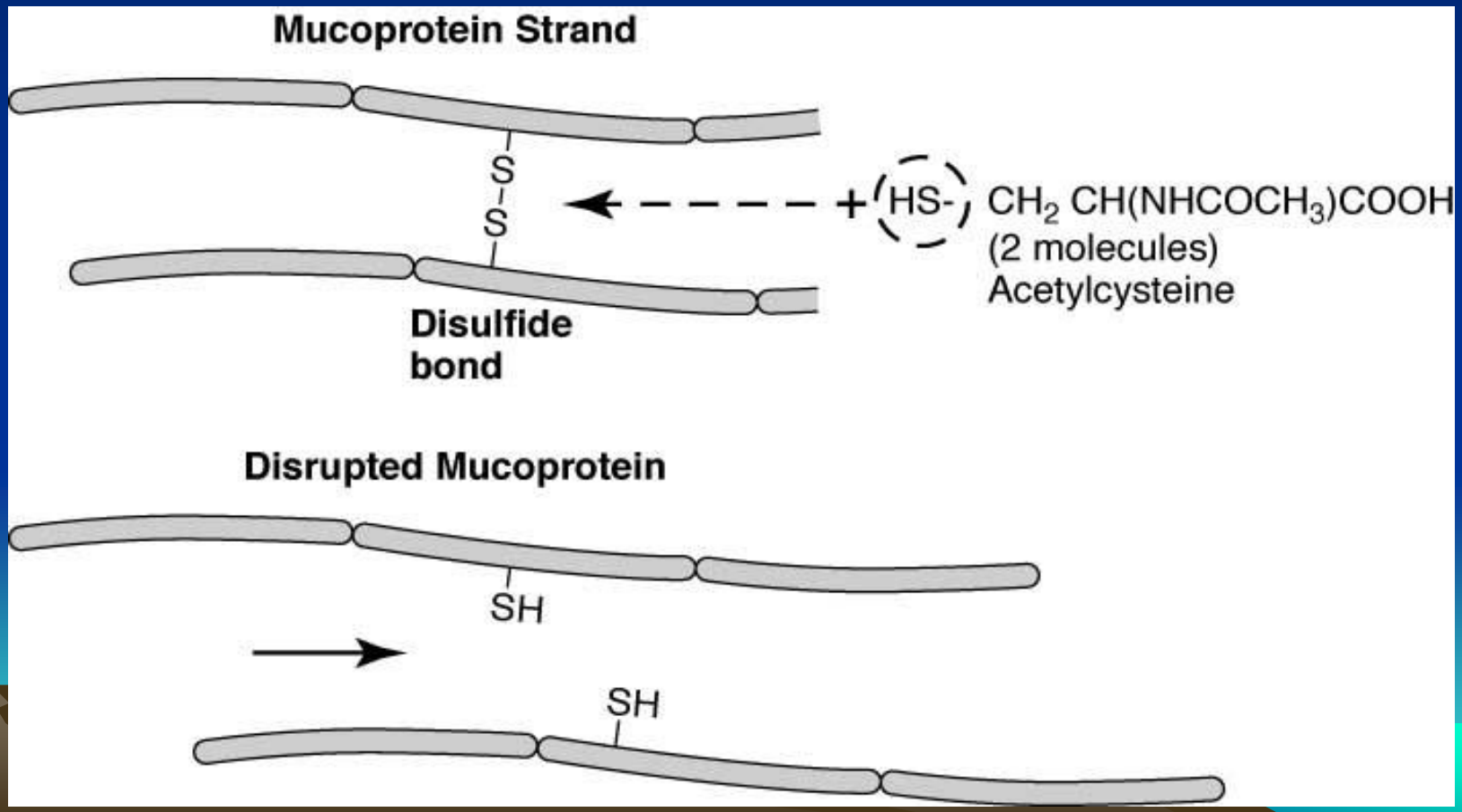
3- Chronic coughing in horses.

4- Bronchopneumonia in cattle.

Mechanism of action:

Disruption of Disulfide Bonds •

Aetylcysteine breaks the bonds by substituting a sulfhydril – radical –HS



Bromhexine

Mechanism of action:

The drug induces the hydrolytic depolymerization of mucous protein fibers of high molecular weight and stimulates the activity of the ciliated epithelium.

It has been shown to reduce the viscosity of bronchial secretions in both animals [and men.

Decongestants:

These are drugs which reduce congestion of congested mucous membranes of nasal passages, reducing tissue edema and secretions by mucous glands.

This is achieved by stimulating α adrenergic receptors on smooth of the blood vessels in mucous membranes and skin → vasoconstriction.

Bronchoconstrictors:

1- These are drugs which stimulate contraction of smooth muscles surrounding the small terminal bronchioles deep with the respiratory tree.

2- They are not used therapeutically because of induction of respiratory dyspnea (difficult breathing).

Causes:

1- Parasympathomimetics:

A- Direct parasympathomimmetics:

Acetylcholine: causing bronchoconstriction and increased bronchial glands secretion.

B- Indirect (parasympathomimmetics) :

Organophosphates: They act by causing irreversible inhibition of cholinesterase enzyme activity → causing ↑ concentration of acetylcholine → bronchoconstriction.

2- Histamine release:

Histamine stimulates H_1 receptors in smooth bronchial muscles → bronchoconstriction.

3- B_2 adrenergic blockers:

The B_2 blockers act by blocking B_2 receptors on bronchial smooth muscles causing → bronchoconstriction.

Bronchodilators:

These are drugs which cause relaxation of bronchial muscles leading to bronchial dilatation.

They are of value in treatment of bronchial asthma and where improved alveolar ventilation is required .

Uses:

1- They are used in mild tracheobronchitis and severe chronic obstructive pulmonary disease in horse.

2- Bronchopneumonia and chronic pulmonary interstitial disease in all species.

3- They are used with or without concurrent corticosteroids therapy for control of chronic bronchitis in dogs and asthma syndrome in cats.

Classification:

1- Parasympatholytics (Antimuscarinc bronchodilators):

a- Atropine:

Its use is limited by its significant side effects on GIT and CNS.

b- Ipratropium bromide:

1- It is an anticholinergic drug used for the treatment of chronic obstructive pulmonary disease and acute asthma.

2- It blocks the muscarinic acetylcholine receptors in the smooth muscles of the bronchi in the lungs, opening the bronchi.

3- It is administered by inhalation for the treatment of chronic obstructive pulmonary disease

2- B2 adrenergic stimulants:

Selective B2 receptors stimulants were preferred to be used to produce bronchodilation.

They include:

A- Selective B2 adrenergic receptors stimulants:

1- Terbutaline:

- It is a synthetic sympathomimetic amine.

-It stimulates B2 specially found in bronchi → bronchial smooth muscles relaxation → bronchodilation.

-It has little effect on B1 receptors.

-It reduces mucous viscosity, increasing the Mucocilliary apparatus affectivity.

2- Albuterol:

-It is a synthetic sympathomimetic amine.

-It stimulates B2 specially found in bronchi (predominant effect) → bronchial smooth muscles relaxation → bronchodilation.

-It has minimal effect on B1 receptors.

-It is used principally in dogs and cats to relieve bronchospasm or cough.

3- <u>Clenbuterol:</u>

-It is a synthetic sympathomimetic amine.

-It is long acting B2 stimulant used to relieve bronchospasm in horses.

-It increases the bronchial secretions, improving **the removal of** bronchial contents by cilliary action.

Older non-selective B adrenergic stimulants:

They include:

1- Isoprotrenol.

2- Ephedrine.

3- Adrenaline.

- They are potent B2 stimulant inducing bronchial smooth muscles.

- They have significant B1 stimulant effect.

- Adrenaline and ephedrine have also α1 adrenergic receptors stimulant effect inducing vasoconstriction.

3- Anti-inflammatory drugs:

Mechanism of action:

The anti-inflammatory effect of short acting corticosteroids such as prednisone and methylprednisolone is important to reduce swelling, edema, inflammation and congestion by inhibiting migration of inflammatory cells to bronchial surface in acute respiratory problems.

Actions:

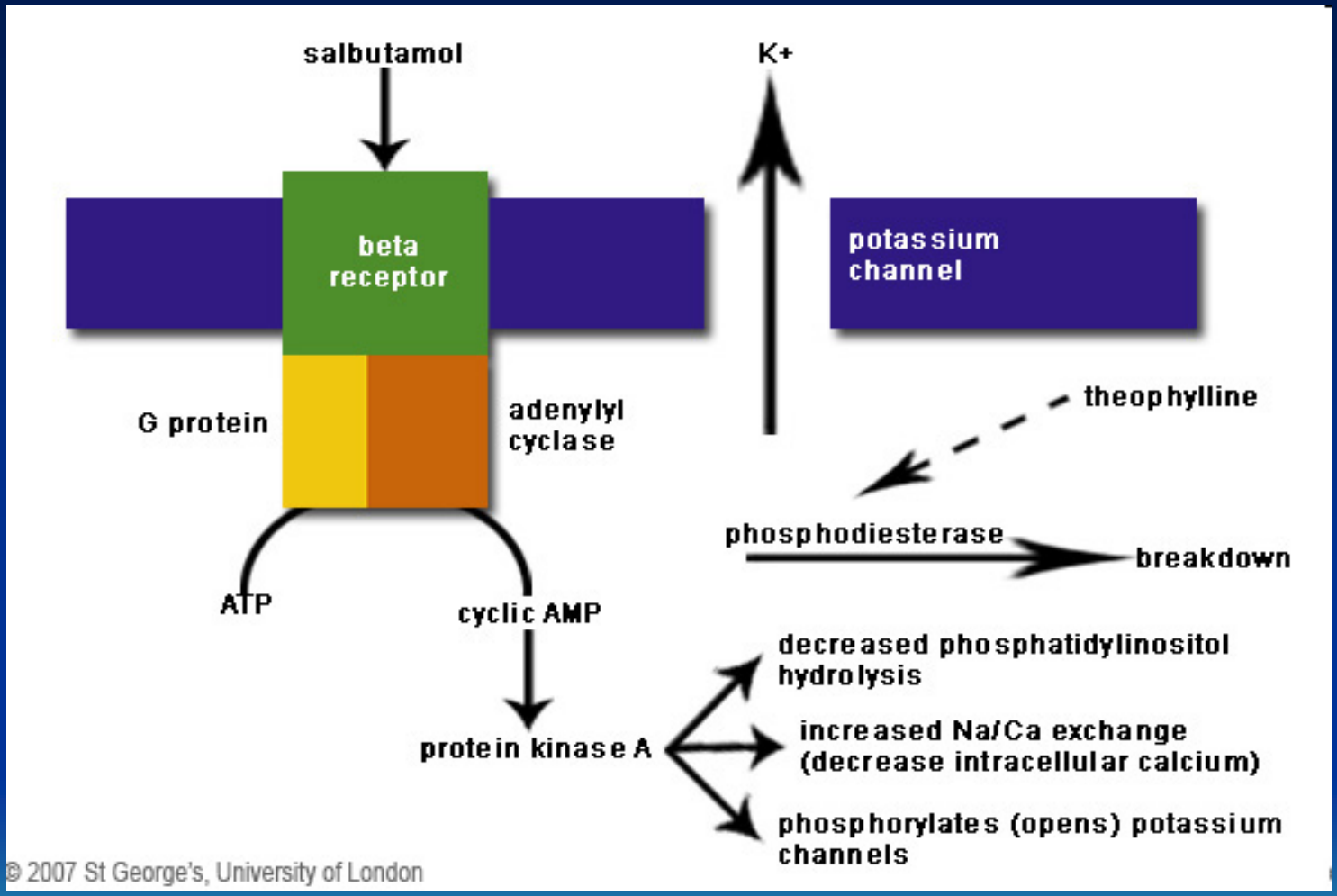
- They improve the activity of Methylxanthines and B adrenergic receptor bronchodilators.
- Large dose of corticosteroids impair the immune system response to infection and delay healing.

4- Methylxanthines:

Methylxanthines are bronchodilators used in the treatment of asthma and chronic obstructive pulmonary disease.

Mechanism of action:

- Methylxanthines act as bronchodilators by relaxing bronchial smooth muscle and helps the constricted airways to dilate.
- The exact mechanism of action with regards to methylxanthines causing bronchodilatation is not well understood but it appears that methylxanthines inhibit the enzyme phosphodiesterase, which degrades cyclic AMP, so methylxanthines tend to increase the concentration of cyclic AMP → accumulate and smooth muscle relaxation continue.


salbutamol
K+
beta receptor
potassium channel
G protein
adenylyl cyclase
theophylline
phosphodiesterase
breakdown
ATP
cyclic AMP
decreased phosphatidylinositol hydrolysis
protein kinase A
increased Na/Ca exchange (decrease intracellular calcium)
phosphorylates (opens) potassium channels
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Preparations:

1- Theophylline (Aminophylline).

2- Etamiphylline.

3 Caffeine.

4- Theobromine.

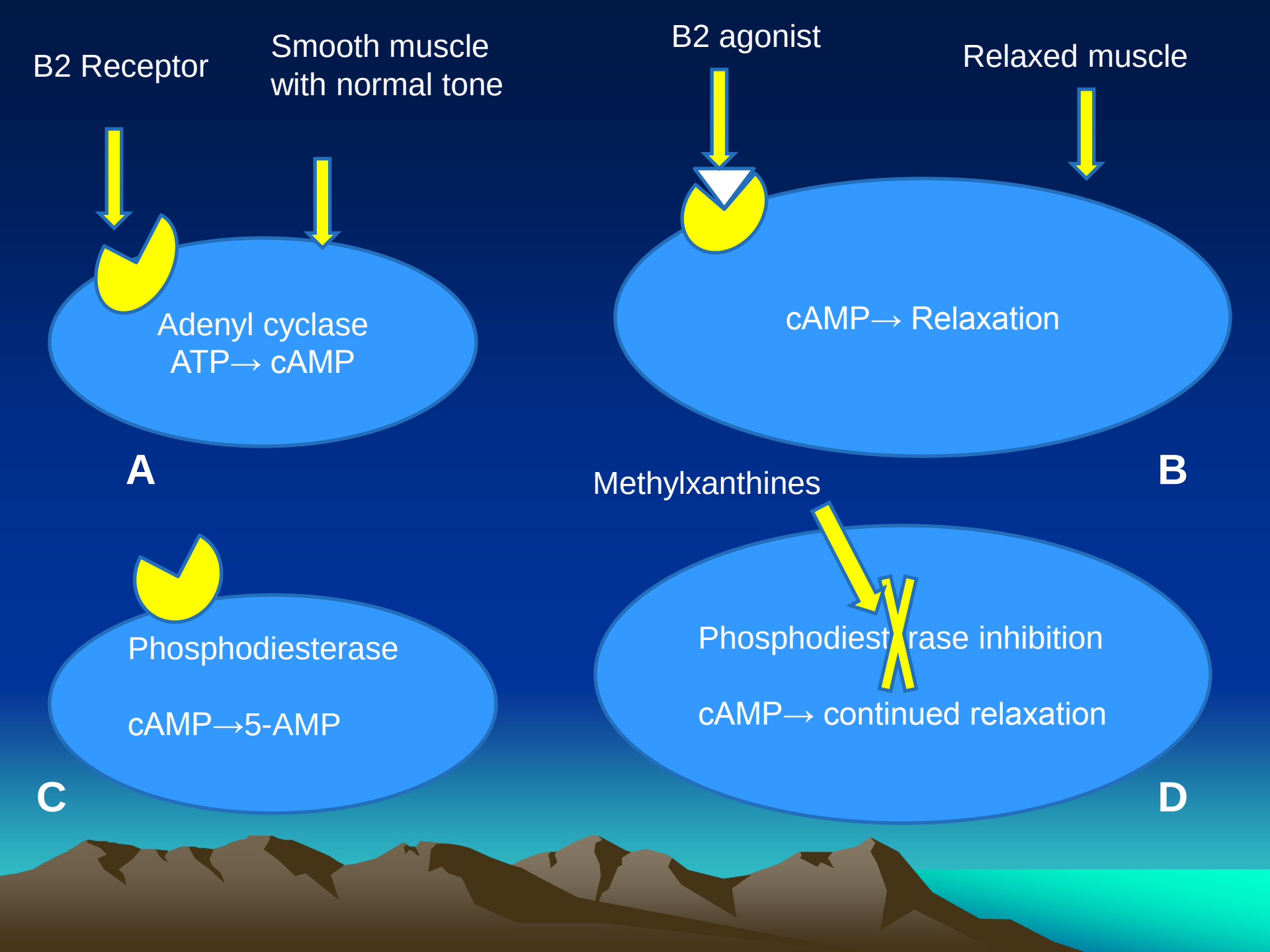
Actions:

1- They are also, CNS, myocardial stimulants and diuretic

2- They stimulate respiratory center in the medulla oblongata.

3- Aminophylline is rapidly absorbed than theophylline because aminophylline composed of theophylline (80%) and ethylene diamine salt (20%) that is responsible for rapid absorption of aminophylline.

4- Methylxanthines are synergistic with B2 adrenergic stimulants in prolongation of bronchodilating effect because B2 adrenergic stimulants stimulate B2 receptors → activation of adenylcyalase enzyme which degrade ATP →↑ cAMP production → bronchodilation and methylxanthines inhibit the activity of phosphodiesterase enzyme activity → block the breakdown of cAMP → thus prolonging or enhancing bronchodilation .


B2 Receptor
Smooth muscle
with normal tone
Adenyl cyclase
ATP→ cAMP
A
B2 agonist
Relaxed muscle
cAMP→ Relaxation
B
Phosphodiesterase
cAMP→5-AMP
C
Methylxanthines
Phosphodiesterase inhibition
cAMP→ continued relaxation
D

Mechanism by which methylxanthines cause bronchodilation:

A- B2 receptor stimulation⟶⟶ increased Adenyl cyclase production and activity with enhance ⟶⟶ production of cAMP.

B- cAMP ⟶⟶ promotes relaxation of smooth muscle inducing bronchodilation.

C- cAMP breaks down by phosphodiesterase enzyme returning the muscle to normal state tension.

D- Methylxanthines inhibit phosphodiesterase , so cAMP is not broken down giving the continuinity of muscle relaxation and bronchodilation.

Important discussions:

Explain whey? (Give reasons):

1- Atropine is rarely used as a bronchodilator for respiratory problems.

This because the atropine administration will block the parasympathetic nervous system → allows the sympathetic nervous system to dominate → producing dry mucous membranes and bronchodilation and reduced effectiveness of mucociliary apparatus, therefore atropine is rarely used as a bronchodilator for respiratory problems except in organophosphate insecticide toxicity in which parasympathetic nervous system is over stimulated.

Explain whey? (Give reasons):

2- Terbutaline and Albuterol are commonly used as bronchodilators than adrenaline.

Answer: This because the use of adrenaline will stimulate the heart and causes vasoconstriction of peripheral blood vessels (↑ the peripheral resistance) and both effects will → ↑ the load on the heart, therefore adrenaline is used only as a bronchodilator for emergency and for short term in hypotension. Meanwhile, Terbutaline and Albuterol are selective B2 stimulant with little B1 stimulant effect→ bronchodilation without cardiac effect.

Explain whey? (Give reasons):

3- It is important to avoid using of antitussive drugs with expectorants.

Answer: This because the use of expectorants will ↑ the fluidity of respiratory secretions and the cough mechanism is needed to remove the extra secretions, therefore blocking the cough reflex with a potent anti-tussive drug will → impair the removal of these secretions.

Explain whey? (Give reasons):

4- Terbutaline can act synergistically with theophylline as a bronchodilator for bronchial asthma.

Answer: This because Terbutaline is B2 adrenergic stimulants stimulate → B2 receptors → activation of adenylcyalase enzyme which degrade ATP →↑ cAMP production → bronchodilation and methylxanthines inhibit the activity of phosphodiesterase enzyme activity → block the breakdown of cAMP → prolonging smooth muscle relaxation, thus prolonging or enhancing bronchodilation .

Explain whey? (Give reasons):

5- In dehydrated animal with non- productive cough, it is important to rehydrate the animal prior to treatment of cough.

Answer: This because rehydration of animal → may change the non-productive cough to → productive cough. It also activate the mucociliary apparatus → improving its function → and the cough may be relieved.

Explain whey? (Give reasons):

6- In respiratory disease, protective inflammatory mechanism cause a complication in such condition. How do you overcome this complication?

Answer: This because inflammatory cell migration into the respiratory tract to overcome the infectious agent or to remove cellular damage. DNA which found in inflammatory cells or cellular debris reacts with mucous to ↑ its viscosity⟶ making it more sticky (forming polymers of glycoproteins linked together by disulfide bond). So, the ciliary apparatus becomes unable to remove these polymerized mucous. This complication can be

counteracted by using Mucolytics (Bromhexine, Acetylcysteine e.t.c. are given orally, by inhalation or by instillation) which have free sulfhydryl groups that open mucoprotein (polymerized mucous) disulfide bonds, reducing the viscosity of mucus. Therefore, facilitate its removal by the cilliary apparatus.