Q9 Describe the mechanism of action of drugs commonly used to treat acute severe asthma (March 2010)

Asthma – a reversible obstruction of the airway due to airways hyperreactivity, bronchoconstriction, airways oedema, inflammatory infiltrates and mucous. Drugs used to treat asthma generally target the bronchoconstriction, inflammatory response and hyperreactivity.

DRUGS TARGETING BRONCHOCONSTRICTION

- **Beta agonists** → bind to the Gs protein of adrenergic B2 receptors and increase adenylyl cyclase and cAMP, causing smooth muscle relaxation. May be rapid onset, short acting (salbutamol) or slower onset, longer acting (salmeterol – more lipophilic which reduces the rate of diffusion away from the target site). SE include tremor and hypokalaemia.
- **Muscarinic antagonists** → bind to the M3 receptor of bronchial smooth muscle, blocking the Gq protein and the associated increase in phospholipase C and intracellular Ca that would normally accompany its activation. This causes smooth muscle relaxation. Generally do not provide sufficient relief on their own, but in conjunction with beta agonists can improve symptoms. May be short acting (ipratropium) or long acting (tiotropium). Can cause dry mouth.
- **Methylxanthines** → eg, theophylline. Act via inhibition of PDE5 and subsequent increase in cAMP → bronchodilation, as well as possible adenosine receptor antagonism. Narrow therapeutic window and risk of arrhythmias and seizure at higher doses – rarely used today.
- **Inhaled adrenaline** → activates beta receptors to provide a similar effect to the beta agonists. It also causes alpha agonism, constricting the bronchial mucosa to reduce airway resistance.

DRUGS TARGETING THE INFLAMMATORY RESPONSE / ARWAYS HYPERREACTIVITY

- **Corticosteroids** → bind to the cell nucleus to inhibit the transcription of genes that encode for inflammatory mediators. Do not directly relax smooth muscle so have little effect in direct bronchorelaxation. Multiple side effects associated including HTN, diabetes, oral candidiasis and gastric ulcers.
- **Antileukotrienes** → eg, montelukast. Competitive antagonist at leukotriene receptors LTD4 and LTE4, reducing leukotriene-mediated bronchoconstriction and inflammatory mediator release
- **Anti-IgE antibodies** → eg; omalizumab. Rarely used; monoclonal antibodies again IgE that reduce the binding of Ige to mast cells and basophils to prevent the allergic reaction. Possilbe increased incidence of malignancy.

OTHER

- **Magnesium** → mechanism unclear but postulated to be actions on calcium channels inducing bronchial smooth muscle relaxation
- **Ketamine** → acts as a bronchial smooth muscle relaxant by inhibiting Ach mediated SM constriction
- **Heliox** → improves airflow by its lower density (as turbulent flow is inversely proportional to the square root of the density of gas)
- **Volatile anaesthetics** → eg, sevoflourane, isoflourane. Thought to act via direct beta agonism plus inhibition of histamine release from mast cells. Can cause hypotension.