

Drug-receptor interaction types



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Drugs and naturally occurring toxins interact with their target molecule at the receptor sites localized in the target molecules. The drug-receptor is highly specific as the drug only binds selectively to a particular receptor. The drug-receptor interacts via several chemical bonds such as covalent bonds, ionic bonds, and hydrophobic bonds (Young et al., 2003). The drugs or toxins have to bind to their target molecules in order to produce its biological functions. In this review, the mechanism of action and effects of ten drugs and naturally occurring toxins will be discussed.

The α -bungarotoxin binds irreversibly to the muscular and neuronal nicotinic acetylcholine receptor (nAChRs) on the post-synaptic membrane thus blocking the depolarization in the post-synaptic site (Young et al., 2003). The α -bungarotoxin antagonize actions of acetylcholine (ACh) which binds to the specific sites in the extracellular region of the ligand-gated sodium channels. Binding of ACh to the specific sites causes conformational change which opens the pore of sodium (Na^+) channels (Patrick & Stallcup 1977). In the absence of ACh, the pores are closed and this prevents end plate potential due to no influx of Na^+ ions (Patrick & Stallcup 1977). Thus, depolarization at muscle cell membrane and the neuromuscular transmission are blocked. When the neuron is stimulated, the contraction of the respiratory muscle will not be able to occur as the signals cannot be transmitted to the muscle (Young et al., 2003). This results in muscular relaxation and paralysis of the respiratory muscles which could also lead to death.

The mast cell degranulating peptide (MCDP) has both inflammatory and anti-inflammatory actions (Stansfeld et al., 1987). At low concentrations, the MCDP mimics the IgE binding sites to the FC ϵ RI mast cell receptor and in the <https://assignbuster.com/drug-receptor-interaction-types/>

absence of IgE, the MCDP binds to the FC ϵ RI mast cell receptor to release histamine (Buku 1998). The MCDP also releases histamine from mast cells in the presence of IgE when a single MCDP molecule cross-links two adjacent IgE molecules at their Fab portions. This cross-link activates the FC ϵ RI receptor causing the cell to degranulate and release histamine (Lorenz et al., 1998). This causes the symptoms of inflammation. At higher concentrations, the MCDP shows anti-inflammatory actions by forming intermolecular disulphide complexes with the IgE. The disulphide will exchange with the readily reduced S-S bonds in the hinge region of the IgE molecule which causes conformational change in the hinge region of the IgE molecule (Ziai et al., 1990). Therefore, when antigen binds the IgE molecule will not be able to transmit histamine-releasing signals to the FC ϵ RI receptor which prevents the release of histamine (Ziat et al., 1990).

Colchicine is an anti-inflammatory drug which is used for treatment of gout as colchicine disrupts the deposition of monosodium urate crystals in the joint tissues of gout patients. The colchicine inhibits the formation and release of chemotactic glycoprotein synthesis during phagocytosis of urate crystals which reduces the chemotaxis and phagocytosis of leukocytes (Molad, 2002). The colchicine also inhibits microtubule self-assembly in neutrophils by binding to tubulin to form tubulin-colchicine complexes and this inhibits the presence of neutrophils in the synovial fluid of the gout arthritis thus reducing the joint inflammation (Hinkley & Green 1971). The colchicine also inhibits the production of tumor necrosis factor alpha (TNF α) which is synthesised by macrophages and down-regulates the expression of

TNF α -receptor on the surface of macrophages and endothelial cells and this shows symptoms of anti-inflammatory activity (Hinkley & Green 1971).

Cholera toxin infects the host cell and binds to the GM1 ganglioside receptor on the (enterocytes) intestinal cells of the host via its pentameric B subunit and this triggers endocytosis of the toxin (Fishman & Atikkan 1980). The A subunit of the toxin consist of two domains (A1 and A2). In order for the A1 domain to become an active enzyme, the cholera toxin must undergo cleavage of the A1 domain from the A2 domain (Cassel & Pfeuffer 1978). The A1 domain of the toxin A subunit will then enter the cytosol thereby activating the G_s α (G protein) via ADP-ribosylation which leads to constitutive activation of adenyl cyclase (Cassel & Pfeuffer 1978). This will give rise to increased cyclic AMP levels inside the host cell. The high levels of CAMP activate the cystic fibrosis transmembrane conductance regulator (CFTR) and this reduces the influx of sodium ions (Cassel & Pfeuffer 1978). In return, this causes dramatic efflux of water from the infected enterocytes which leads to severe diarrhoea and vomiting.

Camptothecin (CPT) inhibits cancerous cells and its molecular target is the human DNA topoisomerase 1 (topo 1). CPT blocks the re-joining of the religation reaction of topo-I by binding at the interface between topo-I and DNA thus, inhibiting topo-I (Kessel, Bosmann & Lohr 1972). This causes the accumulation of the ternary cleavable complex (Hsiang & Liu 1988). The mechanism of CPT cell killing is by S-phase-specific killing via possible collisions between advancing replication forks and topo-I cleavable complexes (Hsiang & Liu 1988). The collision triggers the formation of covalent topo-I DNA complexes. Following collision, three events will occur

which is the formation of double-strand break, irreversible replication fork arrest and the production of topo-I linked DNA break at collision sites (Hsiang & Liu 1988). This attributes to the cytotoxicity of the CPT.

Tetrodotoxin acts by blocking the voltage-gated Na^+ channel in excitatory membranes by binding to the IV domain of the α -subunit at the Na^+ channel pores' vestibule (Hagen et al., 2008). Tetrodotoxin molecule is larger than the Na^+ ion as such the binding blocks the extracellular entry of the Na^+ ion via the Na^+ channel pore. Therefore, influx of Na^+ ions which is essential for the initiation and transmission of signals in excitable membrane are inhibited and the conduction of nerve impulses via the axon and nerve fibres are also prevented (Hagen et al., 2008). The inhibited action potential propagation and depolarization prevents the firing of the affected cell. As such, the sensory and motor neuron functions are disrupted leading to muscular weakness and paralysis (Hagen et al., 2008).

Reserpine controls high blood pressure by acting on vesicular monoamine transporter (VMAT) by binding irreversibly to it. The reserpine irreversibly blocks the VMAT which usually transports the free intracellular catecholamines (monoamine neurotransmitters) in the presynaptic nerve terminal into the presynaptic vesicles which will then be released into the synaptic cleft (Blackman, Campion & Fastier 1979). Thus, when the monoamine neurotransmitter are not transported into the presynaptic vesicles, it will get metabolised by the monoamine oxidase in the cytoplasm and as a consequence of that, the post-synaptic cell cannot be excited (Schuldiner, Liu & Edwards 1993). As the monoamine neurotransmitters are

usually involved in regulating heart rate, the depletion of catecholamines and other monoamine transmitter leads to reduced force of cardiac contraction and peripheral vascular resistance thereby, reducing the blood pressure (Blackman, Campion & Fastier 1979).

Physostigmine is used to reverse the anticholinergic effects by inhibiting the acetylcholinesterase (AChE) enzyme. The physostigmine competitively bind to the acetylcholinesterase to prevent it from degrading acetylcholine after it has been secreted into the synaptic cleft (Triggle, Mitchell & Filler 1998). However, inhibition of physostigmine is temporary, as such the acetylcholine levels will only hike temporarily to overcome the anticholinergic effects (Triggle, Mitchell & Filler 1998). Physostigmine is capable of reversing the antagonism of the central and peripheral acetylcholine as it is a tertiary amine which is able to cross the blood-brain barrier (Triggle, Mitchell & Filler 1998). Physostigmine is most commonly used for the treatment of Alzheimer's disease as brains of individuals with that disease have reduced acetylcholine neurotransmitter levels due to impairment of the cholinergic system (Triggle, Mitchell & Filler 1998). As such physostigmine is used to reverse the anticholinergic effects in individuals with Alzheimer's disease.

Digitalis glycosides binds to the α -subunit of the Na^+/K^+ ATPase pump on the plasma membrane of the cardiac cells. Digitalis causes stabilisation of the Na^+/K^+ ATPase pump in the E2-P transition state, prevents outflow of Na^+ ions thereby increasing the intracellular Na^+ ions (Gheorghide et al., 2004). The ability of the Ca^{2+} ions to get expelled out of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger pump depends on the intracellular concentration of Na^+ ions.

However, as the digitalis prevents the outflow of Na^+ ions, the Ca^{2+} ions will never get pumped out of the cell and this causes the cytoplasmic concentration of Ca^{2+} ions to increase (Gheorghiade et al., 2004). The excess Ca^{2+} ions will cause increased uptake of Ca^{2+} ions into the sarcoplasmic reticulum. The increased Ca^{2+} stores in the sarcoplasmic reticulum will cause activation of the ryanodine receptor by cardiac glycoside and this will further increase release of Ca^{2+} ions from the sarcoplasmic reticulum (Gheorghiade et al., 2004). Thus, more Ca^{2+} ions is available to bind troponin C, increasing heart contraction. The inhibition of Na^+/K^+ ATPase pump in the vascular smooth muscle results in depolarization due to Ca^{2+} influx leading to contraction and vasoconstriction of smooth muscle (Gheorghiade et al., 2004).

Alpha-amanitin (α -amanitin) inhibits RNA polymerase II (Pol II) by disrupting the elongation phase of transcription as it binds tightly to Pol II. The α -amanitin can inhibit Pol II by blocking the translocation of the transcription complex during elongation process or by preventing the phosphodiester bonds which reduces the transcription process proficiency (Bushnell, Cramer & Kornberg 2002). The α -amanitin binds to Pol II under the bridge helix and forms a very strong bond with the bridge helix via its hydroxyproline 2 (Bushnell, Cramer & Kornberg 2002). However, the binding of α -amanitin to the Pol II acts like a barrier to the bridge helix as the binding position of α -amanitin constrains the movement of the bridge helix and this slows the translocation of Pol II complex (Bushnell, Cramer & Kornberg 2002). As the elongation phase is disrupted then production of Pol II gets inhibited.

In conclusion, different drugs and toxins binds specifically to their target molecules and the drug-receptor or toxin-receptor interaction produces specific effects at the target molecules. It is necessary to study the drug-receptor interactions to enable us know the pharmacodynamics and pharmacokinetics of the drugs in the practice of medicine.

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