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## Part ABriefly discuss the signalling process which occurs when salmeterol binds to its targetReceptor

The receptor to which salmeterol binds
The drug salmeterol binds to the active sites of beta-2-adrenergic receptor . This is a category of G protein-coupled receptors. Beta-2-adrenergic receptors have specific actions in the body. They are responsible for the relaxation of smooth muscles relaxation of a non-pregnant uterus, dilation of arteries in the skeletal muscles, contraction of the sphincter muscles and anabolic processes in the skeletal muscle. The receptor has a three dimensional crystallographic structure. The receptors work by ensuring rapid and specific signaling. The receptors couple with Gs G protein, the result being the activation of adenylyl cyclase. The receptors have been established to couple with Gi proteins. This probably provides a mechanism through which the response to ligands becomes extremely localized within body cells (Gruber, 2010).

## The signal transduction process

The G protein-coupled receptors recognize a ligand. Consequently, the structure of the receptor is altered leading to the inactivation of the G protein. This causes the alpha G to bind itself to the GTP molecule. Simultaneously, it dissociates from the two subunits of the G-protein. This is what exposes the sites on the protein subunits that are capable of interacting with other molecules. The subunits of the G protein that are detached from the receptor initiate the signaling process from many effector proteins and ion channels. The ion channels permit the release of other messenger molecules. The strength of signal amplification caused by G protein coupled receptors is dependent on the lifetimes of the receptor-effector protein complexes ligand-receptor complexes and the time taken by the intrinsic enzyme activity to deactivate the receptors and effectors (Robert, 2007)

## Molecular reasons for the onset of action of salmeterol

Salmeterol has long lipophilic side chains that bind to exosites that are close to the beta-2-receptors on the bronchiolar smooth muscles and in the lungs. This allows the active part of the drug molecule to remain attached to the receptor site continuously binding and releasing. The stimulation of the beta-2-receptor in the lungs results in the relaxation of the smooth muscles of the bronchus. This is followed by bronchodilation thereby causing increased bronchial airflow. Unlike formoterol, salmeterol has a slower onset of action because of its higher lipophilicity. This is because the drug has a functional group called aryl alkyl group. This functional group has a chain length composed of eleven atoms from the amine. As such, the bulkiness of the drug makes the compound increasingly lipophilic. the onset of the action is also unlike other drugs of the same class of salmeterol because its molecules make the beta receptor selective (Aalbers et al, 2012)
Salmeterol has also a characteristic long duration of action. This is as a result of of the molecules primarily diffusing inside the plasma membrane of the cells in the lungs. The molecules are then released back to the exterior of the cell slowly. They react with the beta-2-adrenoceptors resulting in the formation of the anchor membranes by the long carbon chains from the aryl alkyl group. The fact that the molecules are absorbed into the plasma membrane before they can be released back where they can meet the beta-2-adrenoceptors contribute to the slower onset of action compared to other drugs of the same class. The plasma membrane is made of a lipid layer. Since the drugs are more lipohillic that other drugs of the same class, the diffusion into the plasma membrane takes longer. This delays the onset of action (Aparici et al., 2012)

## Part B

Comparing and contrasting the pharmacokinetics parameters of Bendroflumethazide, Hydrochlorothiazide and Metolazone
Absorption
The oral absorption of metolazone at 64% is considerably lower compared to that of hydrochlorothiazide at 65-75%. The absorption of hydrocholothiazide in patients suffering from congestive heart failure is reduced. Of the three drugs, Bendroflumethazide is the most readily absorbed. The drug is a hundred percent bioavailable after oral administration. The three drugs are similar in that they are primarily absorbed orally after administration. The formulation of the drug is a prominent influence on the rate of absorption. For instance, the peak blood levels of the drug are obtained after two to four hours of oral administration depending on the formulation (Chan & Peterson, 2012).

## Distribution

More than 90% of bendroflumethazide is bound to plasma proteins. This is considerably higher compared to the 50% of hydrochlorothiazide that is bound to plasma proteins. Unlike the other two drugs metolazone has protein binding of 33%. Only about 2-5% of the drug is unbound and in circulation. About 50-70% of metolazone is bound to erythrocytes. The volume of distribution for metolazone is one hundred and thirteen liters compared to two liters per kilogram of hydrochlorothiazide. 90-95% of the drug is bound to the red blood cells (Jing-He. et al., 2012).

## Metabolism

Bendroflumethazide is fairly extensively metabolized in the body after administration. Metolazone on the other hand is not as extensively metabolized as bendroflumethazide. It is established that the only 35. 5% give or take 4. 5% of the drug is metabolized. Unlike bendroflumethazide and metolazone, hydrochlorothiazide is not metabolized in the body. The drug is rapidly excreted in the kidneys after oral administration (Musini et al., 2012)

## Elimination

As espoused above, hydrochrolothiazide is not metabolized in the body but eliminated quickly by the kidneys. It crosses the placental barrier but cannot cross the blood-brain barrier. It is excreted through breast milk. Unlike hydrochlorothiazide, metolazone and bendroflumethazide are both excreted in urine. Renal elimination contributes to over 90% of the elimination of metolazone. 30% of bendroflumethazide is eliminated unconverted in urine (Sharma, 2012).

## Relationship between the pharmacokinetics of the drugs and the recommended dosage regimens

The once a day recommended dosage regimen for metolazone is due to the pharmacokinetics property of the drug to bind to proteins thereby cause a prolonged or extended duration of action. Before the drug activates the actives its of the receptors for signaling, it is first absorbed into the plasma membrane of proteins. It is then released slowly and for a long period of time (Georges et al., 2012). As such, the drug is not eliminated as rapidly because of the slow release. This is the case for bendroflumethazide that has 90%of the drug bound to plasma proteins. The same mechanism gives it a long duration of action, hence the recommended once a day dosage regimen. Hydrochlorothiazide is not metabolized in the body. It also crosses the placental barrier. This relates to the single recommended dose . The accumulation of the drug in red blood cells also contributes to this.

## A comparison and the contrast of the side effects of the drugs

One common side effect of the drugs is exfoliative dermatitis or some form of skin rash characterized by peeling of the skin. Muscle weakness and fatigue also cuts across the board. While bendroflumethazide causes increased urination, metolazone causes less than usual urination or at times no urination at all (Suter et al., 2012). As such, dehydration is a factor to consider when dispensing these drugs. Other factors to consider include lung infections and fluid in the lungs, side effects associated with bendroflumethazide. Other minor side effects include dizziness that is indicated in metolazone and bendroflumethazide. Uneven heartbeat is indicated in metolazone and hydrochlorothiazide and not in bendroflumethazide (Stears et al., 2012). As such, it is important for physicians and chemists consider such factors when choosing an appropriate drug for an individual (Ovakim et al., 2012).

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