Albuterol: Effects on the Beta-2 Receptor

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Abstract

Asthma is a chronic airway disease that inflames and narrows the bronchi and bronchioles, thus making breathing very difficult. The absolute etiology of asthma is unknown but hereditary, food and environmental allergens seem to play significant roles in its onset. Unfortunately, there is no cure for asthma. Management focuses on treating symptoms in acute events and avoiding known triggers. The standard treatments are bronchodilators and steroids[1].

Case Study

Patient BC is a 7-year-old male who presents to the ER with severe respiratory distress symptoms consistent with a severe asthma exacerbation. Upon assessment, the patient has a fast heartbeat, is sweating, and has an I:E ratio of 1:4 inspiration to expiration. An X-ray shows inflamed and severely constricted lungs. When asked, the mother confirms that symptoms began the previous night and the patient's symptoms have not responded to his albuterol metered dose inhaler. The patient is given high dose albuterol via a nebulizer treatment over 1 hour repeated twice. Staff worries that administration of albuterol may worsen the patient's tachycardia, or fast heartbeat.

Introduction

Epinephrine is the body's natural ligand and full agonist at the β_2-receptor, which exists in an inactivated and activated state[2]. The inactivated state predominates[3]. The activated β_2-receptor leads to a complex cell-signaling pathway resulting in an increase of cAMP and subsequent inhibition of intracellular calcium release. This reduction of intracellular calcium levels leads to relaxation of the bronchioles and dilation of the airways. Albuterol is similar functionally and structurally to epinephrine. Albuterol is a short-acting partial β_2-agonist[2]. Short-acting β_2-agonists are indicated for acute asthma symptoms and for prevention of exercise-induced asthma[4]. Albuterol treats asthma by relieving airway constriction through binding of the G-protein coupled β_2-receptor.

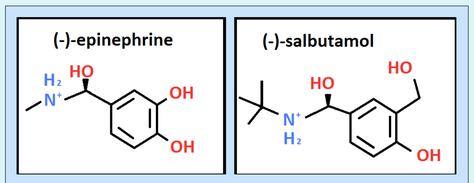

Figure 1. Molecular structure of epinephrine and albuterol[5].

In heart tissue, increased levels of cAMP have chronotropic and inotropic effects via the β_1-receptor[3]. For this reason, treatment requires selective activation of the β_2-receptor. There is 65-70% homology between β_1 and β_2-receptors, which leads to tachycardia as a side effect[3]. This is more of an issue with older β_2-agonists, such as metaproterenol and isoproterenol[4]. Throat irritation and upper respiratory tract infections are also common side effects. Metabolic effects and tremor are typically not a problem with inhaled albuterol in normal doses. Drug-drug interactions are usually not a concern with inhaled albuterol. In addition, albuterol has a longer duration of action (4 to 6 hours) than metaproterenol and isoproterenol[4].

Molecular Story

Drug Target

- The **binding site** is a β_2-adrenergic receptor in the lungs. It is a G-protein coupled receptor (GPCR), which is a transmembrane receptor[2]
- The **ligand binding site** is inside the barrel formed by the 7 transmembrane helices of the GPCR

Albuterol

- Short-acting β_2-adrenergic receptor agonist
- Exists as a racemic mixture: equal amounts of the (S)- and (R)-enantiomers

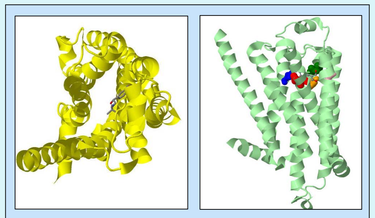

Figure 2. Top view (left) and side view (right) of the G-protein coupled β_1AR-m23receptor bound to (R)-albuterol[6].

How Albuterol Binds[3]

- Five critical amino acids on the binding site of the receptor appropriately align with the corresponding sites on the albuterol molecule
- The orientation of the (R)-albuterol enantiomer molecule allows for these interactions, resulting in activation of the β_2-receptor
- The (S)-enantiomer does not align properly in the binding site, leaving it as the less preferred enantiomer

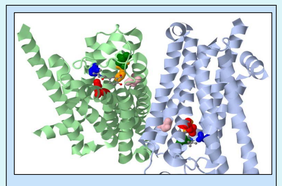

Figure 3. Ribbon structure of two (R)-albuterol molecules bound to two β_1AR-m23 receptor sites. Receptor amino acids are colored[6].

How Albuterol functions

- Reaches the β_2-adrenergic receptors in the lungs through inhalation of the medication
- Sympathomimetic response of relaxing smooth muscles and relieving bronchospasm
- Side effects caused by stimulation of β_1-adrenergic receptors in the heart include racing heart and jitters[4]

The (R)-albuterol molecule[2]

- Three domains that interact with amino acids in the binding site:
  - *Secondary amine*: serves as a hydrogen bond donor with Asn329 and as a hydrogen bond acceptor with Asp121
  - *Hydroxyl group*: interacts with Asp121 as a hydrogen donor and with Asn329 as a hydrogen acceptor
  - *Catechol ring*: interacts with three different amino acids

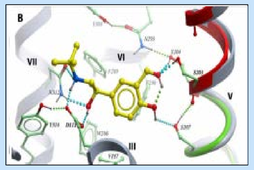

Figure 4. Structural modeling of albuterol bound to the β_2 receptor[5].

- π-π interaction between the catechol ring and Phe307 of the receptor
- Van der Waals interactions with the catechol ring and the neighboring chains in the receptor
- hydrogen bond between *para*-hydroxyl group on catechol ring and Ser211
- hydrogen bond between *meta*-hydroxymethyl group on catechol ring and Asn310
- (R)-albuterol acting as the hydrogen donor in both hydroxyl reactions

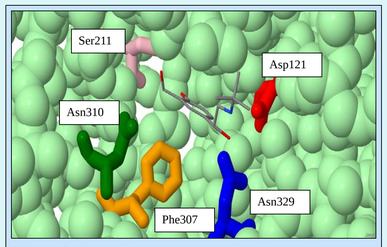

Figure 5. Space-filled structure of the interacting amino acids of β_1AR-m23 receptor[6].

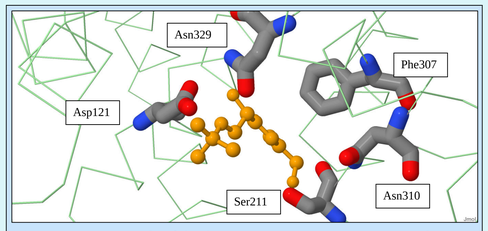

Figure 6. Amino acids of the β_1AR-m23 receptor interacting with (R)-albuterol (in orange)[6].

Further Research

Albuterol causes off-target effects on β_1-receptors in the heart leading to tachycardia. Future research should identify an antagonist to reduce or prevent tachycardia after albuterol administration. One study successfully utilized magnesium sulfate to prevent tachycardia after administration of salbutamol[7].

Another option is to utilize the R enantiomer, levalbuterol. Levalbuterol has higher affinity for the β_2-receptors in the lungs. Research has shown statistically significant reductions in tachycardia with this enantiomer[8,9].

Improvements to the albuterol structure should not alter the catechol ring structure, amine group, or hydroxyl group.

Summary

β_2-agonists dilate bronchioles resulting in increased air flow. Some adverse effects associated with albuterol are tachycardia, tremor and agitation[10]. However, the benefits far outweigh the adverse effects as an asthma attack can be life-threatening[11].

The staff pharmacist recommended albuterol to the medical team because it causes bronchiole dilation and airway relaxation, thus improving the patient's ability to breathe. However, albuterol can exert off-target effects on other beta receptors at higher doses, so the minimum effective dose should be used[3,10]. Albuterol is not recommended as a daily asthma control agent. For this reason, the patient will need appropriate asthma control medications before being discharged from the hospital[3].

Upon discharge the patient should be counseled on management of asthma. A long acting β_2-agonist like salmeterol should be prescribed with a corticosteroid. Albuterol should be prescribed as a rescue inhaler. A leukotriene pathway inhibitor may also be prescribed[11]. If the patient is compliant and their asthma is well controlled, they should not have to use their albuterol rescue inhaler often. The patient should be educated about asthma attack triggers and the importance of medication compliance in order to prevent future attacks.

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