Salbutamol-Induced Desensitization and Attempts to Resensitize In Vitro

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ABSTRACT

The study was carried out to desensitize spontaneously active isolated chick rectum with salbutamol in log doses starting from 100 nanogram and resensitize with various drugs as a result to revive the desensitized tissue and respond to Salbutamol. The tissue response after desensitization to alpha, beta adrenergic and muscarinic acetylcholine receptor antagonists was isotonically recorded for 10 minutes using thermostatically-controlled organ bath with aeration. The results with prazosin showed that the tissue recovered from desensitization and exhibited spontaneous motility and responded to salbutamol faster.

Keywords: Salbutamol, Chick rectum, Desensitization, Prazosin, Resensitization

Asthma, from the Greek (asthma) meaning gasp, is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, intolerance [1-4], an increase in airway hyperactivity, airflow obstruction and bronchial spasm. Symptoms and even increased mortality [5]; effects which may be include wheezing, coughing, chest tightness and secondary to beta2-AR desensitization. SABAs are the shortness of breath. Medications used to treat asthma remainstay for the acute symptomatic treatment of asthma are divided into 2 general classes: and provide effective bronchial protection to a wide range of bronchial constrictor agents. By using these symptoms including Short acting beta-2 agonists medicines too frequently, the efficiency may decline, (SABA) such as salbutamol (Albuterol), producing desensitization resulting in an exacerbation of symptoms which may lead to refractory asthma and death. LABAs are similar in structure to SABAs but further exacerbations including inhaled corticosteroids have much longer side chains resulting in a 12-hour duration such as hydrocortisone and beclomethasone; inhaled effect. While patients report improved symptom control, long acting beta-2 agonists (LABA) such as salmeterol these drugs do not replace the need for routine rescuers and formoterol; inhaled anti-cholinergics such as salmeterol and their slow onset means the short acting dilators are ipratropium and tiotropium; leukotriene modifiers such still be required. However for the past 4 decades, there as montelukast and zafirlukast; mast cell stabilizers such has been a continuing debate concerning whether as sodium cromoglicate and nedocromil sodium; methyl regular chronic treatment with these drugs may be doing xanthenes such as theophylline and immunomodulators more harm than good [8]. In 2005, the USFDA released such asomalizumab, a health advisory alerting the public to findings that Beta-2-adrenoceptor (beta2-AR) agonists are the show the use of LABA could lead to worsening of most-commonly used bronchodilators in both the acute symptoms and in some cases death. In 2008, members of USFDA recommended withdrawing approval for chronic mono-therapy with long-acting and/or short-term bronchodilators as a result to revive the desensitized tissue and respond to Salbutamol. The tissue response after desensitization to alpha, beta adrenergic and muscarinic acetylcholine receptor antagonists was isotonically recorded for 10 minutes using thermostatically-controlled organ bath with aeration. The results with prazosin showed that the tissue recovered from desensitization and exhibited spontaneous motility and responded to salbutamol faster.

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new safety requirements for LABA that is, use of LABAs are contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid. Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone. The role of beta-2 adrenoceptor in both the pathogenesis and treatment of asthma has become a subject of intense speculation and investigation for the last 25 years. This study was carried out to resensitize the salbutamol-induced desensitization in spontaneously active isolated chick rectum.

**MATERIALS AND METHOD**

**Animals**

Freshly-removed intestine of chick slaughtered at a local chicken shop was immediately put into cold 500 ml Krebs solution, transferred to laboratory and aeration provided immediately.

**Methods**

The rectum, the end part of the gastrointestinal tract, was identified; 2-3 cm portion was cut and trimmed off from the mesentery and other tissues. Krebs solution was slowly passed through the lumen to flush out any contents. The rectum was mounted in a thermostatically controlled organ bath and aerated. The tone of the tissue went up to half the original baseline. Salbutamol (30 µg) produced relaxation, with washings the tone regained its baseline. As shown in Fig 2, salbutamol (10 µg) produced a brief contraction followed by relaxation, salbutamol (300 µg) produced slight relaxation. Salbutamol (1 mg) did not produce any response showing desensitization (Fig 1).

**Drug Solutions**

- Tyrodes solution (composition: sodium chloride 8.0 gm, potassium chloride 0.2 gm, magnesium chloride 0.1 gm, calcium chloride 0.2 gm, sodium bicarbonate 1.0 gm, dextrose 1.0 gm, distilled water 1 litre).
- Krebs solution (composition: sodium chloride 6.9 gm, potassium chloride 0.35 gm, calcium chloride 0.28 gm, sodium bicarbonate 2.1 gm, magnesium sulphate 0.29 gm, potassium/sodium di-hydrogen phosphate 0.15 gm, dextrose 2.0 gm, distilled water 1 litre).

Salbutamol obtained as Asthalin respiratory solution purchased from drug store and prepared dilutions of 100ng, 300ng, 1µg, 10 µg, 30 µg, 100 µg, 300 µg and 1mg using distilled water. Prazosin tablets purchased from local drug store, dissolved in distilled water, filtered and prepared different concentrations in micrograms.

**RESULTS**

Salbutamol (SAL) in log dose range of 100 ng to 30 µg produced dose dependent relaxations; 100 µg of salbutamol produced initial contraction followed by relaxation. Salbutamol (300 µg) produced slight relaxation. Salbutamol (1 mg) did not produce any response showing desensitization (Fig 1).

As shown in Fig 2, salbutamol (10 µg) produced a brief contraction followed by relaxation, with washings the tone did not regain its baseline. Salbutamol (100 µg) did not produce any response showing desensitization. Salbutamol in log doses starting from 100 nanogram for 1 min each to record the tissue responses, until tissue relaxation, with washings the tone regained its baseline stopped responding which is said to be desensitized. 10 µg salbutamol produced prominent relaxation. With washing, the tone did not rise and finally (PRA) in different microgram concentrations were salbutamol 10 µg produced slight relaxation. Second observed for 5-10 minutes. Finally, once the tissue dose of prazocin (10 µg) reproduced tone and motility, regained the original baseline and motility which can be salbutamol 10 µg produced relaxations. Prazocin (30 µg) did not produce any response, with wash, the tone went up.

**Fig 1.** Effect of various concentrations of salbutamol (SAL) on isolated chick rectum in vitro

**Fig 2.** Effect of salbutamol (SAL) on isolated chick rectum and influence of prazocin (PRA) in vitro

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As shown in Fig 3, salbutamol (3 μg) produced slight relaxation, with washings the tone did not regain to the baseline. Subsequent addition of two doses of salbutamol (10 μg) produced slight relaxations. Prazocin (10 μg) produced tone and motility and in the presence of prazocin, SAL (10 μg) produced relaxations. Similarly prazocin in several fixed doses of 30 μg and a single dose of 10 μg produced tone and motility, followed by prominent relaxation with salbutamol (10 μg). Continuing in second tracing in the Fig 3, four doses of salbutamol 30 μg were added with intermittent washings, the first dose did not produce any response, the second dose produced some relaxation, third and fourth doses did not produce any response. Prazocin (30 μg) did not produce any response, a second higher dose of prazocin (100 μg) produced tone and motility in the presence of 10 μg salbutamol-produced relaxation.

Similarly prazocin in different doses was added and produced tone and motility and in its presence salbutamol-produced relaxations.

As shown in Fig 4, first dose of 10 μg salbutamol produced relaxation; second dose of salbutamol (10 μg) produced slight relaxation. Subsequent three cumulative doses of 10 μg salbutamol did not produce any response could be due to desensitization. Prazocin (100 μg) did not produce any response, second dose of 30 μg prazocin produced contraction. Salbutamol (10 μg) produced relaxation. Subsequent addition of three cumulative fixed doses of 10 μg salbutamol did not produce any response but the tone fell down. Two sets of prazocin and cumulative doses of salbutamol produced contractions followed by relaxations respectively.

Fig 3. Effect of salbutamol (SAL) on isolated chick rectum and influence of various concentration of prazocin (PRA) in vitro

Fig 4. Effect of cumulative doses of salbutamol (SAL) on isolated chick rectum and influence of various concentration of prazocin (PRA) in vitro

DISCUSSIONS

Salbutamol produced desensitization at beta-2 receptor in Fig 1. Many of our experiments showed that salbutamol is not specific beta-2 adrenergic receptor agonist, it acts on both alpha and beta receptors i.e., producing immediate contraction followed by a slower relaxation and this could be the component which is responsible for sudden deaths in asthma patients [9-14]. Salbutamol produced response by acting on alpha-1 and beta-2 receptors till receptor saturation, Prazosin per se produced tone and motility, and it seems to facilitate relaxation. Combination of salbutamol-prazosin by alternate administration showed beneficial effects. This is fairly satisfactory combination which might help in preventing the desensitization. The numerous experiments are quite supportive that salbutamol and prazosin combination could be a suitable combination in the therapy of asthma. The actual mechanism involved in tissue resensitization is subject of further research.

It is concluded that to certain extent we succeeded in achieving our goal of finding out the possible combination of prazocin with salbutamol which can help the asthma patient in getting relief without any danger or emergencies.

REFERENCES


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