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 gashp, is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, an increase in airway hyper-responsiveness to allergen [1–4], poor asthma control [6] and even increased mortality [7]; effects which may be included wheezing, coughing, chest tightness and secondary to beta2-AR desensitization. SABAs are the shortness of breath. Medications used to treat asthma mainstay 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 have much longer side chains resulting in a 12-hour such as hydrocortisone and beclomethasone; inhaled effect. While patients report improved symptom control, long acting beta-2 agonists (LABA) such as salmaterol these drugs do not replace the need for routine rescuers and formoterol; inhaled anti-cholinergics such as 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 are montelukast and zafirlukast; mast cell stabilizers such has been a continuing debate concerning whether beta, sodium cromoglicate and nedocromil sodium; methyl regular chronic treatment with these drugs may be done xanthenes such as theophylline and imunomodulators more harm than good [8]. In 2005, the USFDA released such asomalizumab. A health advisory alerting the public to findings that Beta2-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 rescue and maintenance therapy of asthma. However, of USFDA recommended withdrawing approval for chronic mono-therapy with long-acting and/or short-term medications in children. In 2010, USFDA gave
new safety requirements for LABA that is, use of
LABAs are contraindicated without the use of an
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 aerated
provided immediately.

Methods
The rectum, the end part of the gastro-intestinal
tract, was identified; 2-3 cm portion was cut and
transferred into Petri dish containing Krebs solution.

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
transferred into Petri dish containing Krebs solution,
relaxation. Salbutamol (1 mg) did not produce any
trimmed off from the mesentery and other tissues. Krebs
response showing desensitization (Fig 1).

solution was slowly passed through the lumen to flush
out any contents. The rectum was mounted in a
brief contraction followed by relaxation; with washings
thermostatically controlled organ bath and aerated. The
tone of the tissue went up to half the original
tissue response was isotonically recorded (tension
weight 1 gm, magnification 10 times) in non-cumulative
and cumulative manner that this tissue invariably had
Salbutamol (100 µg) did not produce any response
showing desensitization. The rectum was exposed to
Salbutamol in log doses starting from 100 nanogram for
tone and motility, then 10 µg salbutamol produced some
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.
and 10 µg salbutamol produced prominent relaxation.
Continuing further, tissue responses with prazosin
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
and subsequent doses of 10 µg, 30 µg and 100 µg
resensitized, salbutamol in microgram concentrations
salbutamol produced relaxations. Prazocin (30 µg) did
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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Fig 3. Effect of salbutamol (SAL) on isolated chick rectum and influence of various concentration of prazocin (PRA) in vitro

and finally prazocin 100 μg did not produce any response.

As shown in Fig 3, salbutamol (3 μg) produced relaxation, with washings the tone did not regain to 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 and 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. It 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 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 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


14. Current Author Addresses

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