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, airway hyper-responsiveness to allergen, poor asthma control, airflow obstruction and bronchial spasm. Symptoms may include wheezing, coughing, chest tightness and dyspnea. LABAs are the most commonly used bronchodilators in both the acute and chronic treatment of asthma. However, for the past 4 decades, there have been a continuing debate concerning whether long acting beta-2 agonists (LABA) such as salmeterol and formeterol; inhaled anti-cholinergics such as ipratropium and tiotropium; leukotriene modifiers such as montelukast and zafirlukast; mast cell stabilizers such as sodium cromoglicate and nedocromil sodium; methylxanthines such as theophylline and imunomodulators have much longer side chains resulting in a 12-hour range of bronchial constrictor agents. By using these medicines too frequently, the efficiency may decline, producing desensitization resulting in an exacerbation of symptoms which may lead to refractory asthma and even increased mortality. LABAs are similar in structure to SABAs but further exacerbations including inhaled corticosteroids have much longer side chains resulting in a 12-hour secondary to beta2-AR desensitization. SABAs are the shortness of breath. Medications used to treat asthma instead of chronic treatment with these drugs may be doing even increased mortality. In 2008, members of USFDA recommended withdrawing approval for these medications in children. In 2010, USFDA released a health advisory alerting the public to findings that most-commonly used bronchodilators in both the acute symptoms and in some cases death. In 2008, members of USFDA recommended withdrawing approval for rescue and maintenance therapy of asthma. However, in 2010, USFDA gave
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-
duced 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 gastro-intestinal
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
bath; with washings the tone did not rise and
then subsequent doses of 10 μg, 30 µg and 100 µg
produced relaxations. Prazocin (30 µg) did
not produce any response, with wash, the tone went up

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
salbutamol in log doses starting from 100 nanogram for
1 min each to record the tissue responses, until tissue
regained its baseline and motility which can be
observed for 5-10 minutes. Finally, once the tissue
regained the original baseline and motility which can be
resensitized, salbutamol in microgram concentrations
produced relaxations. Prazocin (30 µg) did
not produce any response, with wash, the tone went up

RESULTS

As shown in Fig 2, salbutamol (10 µg) produced a
brief contraction followed by relaxation; with washings
the tone went up to half the original
tone and motility, then 10 µg salbutamol produced some
1 min each to record the tissue responses, until tissue
regained its baseline
stopped responding which is said to be desensitized.

Continuing further, tissue responses with prazosin
in different microgram concentrations were
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
resensitized, salbutamol in microgram concentrations
produced relaxations. Prazocin (30 µg) did
not produce any response, with wash, the tone went up

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
mg, 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, 3 µg, 10 µg, 30 µg, 100 µg, 300 µg
diluted using distilled water. Prazosin tablets
purchased from local drug store, dissolved in distilled
water, filtered and prepared different concentrations in
micrograms.
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 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.

**References**


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