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Adrenoceptors, Pulmonary Circulation and Pulmonary Compliance in the Anaesthetized Cat

R.K. Kotoh - Mortty [1]

Summary

In asthma, the salutary effect of bronchodilators derives from their decreasing pulmonary resistance which is invariably, accompanied by an increase in pulmonary compliance. In an anaesthetized cat a state of experimentally-induced broncho-constriction, bronchodilators cause a decrease in pulmonary resistance in an increase in pulmonary compliance. The effects of bronchodilators are accompanied by changes in systemic and pulmonary arterial pressure. Drug-induced changes in the diastolic pulmonary pressure of such a cat were found to be associated with opposite changes in pulmonary compliance. However, no clear-cut inter-relationship could be drawn between changes in pulmonary compliance and concomitant alterations in pulmonary vascular pressure. This suggests that additional factors may play a part in drug-related changes in pulmonary compliance.

Introduction

The bronchodilator effects of the sympathomimetic amines-manifested in their reduction in pulmonary resistance and increase in pulmonary compliance in an asthmatic condition is attributable to the mediation of their pharmacological action through B-Adrenoceptors. Whereas there is evidence for the involvement of B_2 adrenoceptors in reduction in airway resistance, the involvement of B-adrenoceptors in the increase in pulmonary compliance is not clearly established. Airways resistance is the change in driving pressure per unit change in airflow or the degree of obstruction offered by the conducting airways to airflow; pulmonary compliance, on the other hand, involves the distensibility of the peripheral airways, that is, it is the change in lung volume per unit of pressure change.

This experiment aims to investigate the relationship that may exist between the effects of various drugs on pulmonary compliance and pulmonary arterial pressure and, to determine to what extent the adrenoceptor types in the pulmonary vessels may affect their alterations in pulmonary compliance. Evidence so far accumulated has indicated the presence of a predominantly alpha-adrenoceptor population in the pulmonary circulation in the dog, rabbit, calf, guinea-pig and man (1, 2, 3, 4) which mediate vasso-constriction. More yet is to be known about the adrenoceptor population in the pulmonary vessels of the cat. Although much pharmacological information on extra pulmonary blood vessels has recently become available from which some generalizations may be made, it is worthy to note that blood vessels are highly heterogeneous in their response to drugs (5, 6). Thus Williams (7), Bevan (8), Buffolo and

[1] Department of Pharmacology, University of Science and Technology Kumasi, Ghana.

Waddel (9), and Misu, Kaiho, Ogawa and Kubo (10) also noted the heterogeneity of various mammalian vascular vessels in their response to sympathomimetic a mines. Experimental results from *in vitro* work could permit only limited prediction of pharmacological characteristics of a short segment of a blood vessel, much less of an entire vascular system.

An increase in pulmonary compliance is known to decrease pulmonary vascular pressure and vice versa (11). If the pulmonary vessels in the cat have any appreciable B-adrenoceptor population, then it is conceivable that the B-adrenoceptor agonists and antagonists would have an indirect effect on pulmonary compliance by their action on pulmonary vascular pressure.

Materials and Methods

General

The experiments were performed on four adult cats of either sex which were anaesthetized by an intraperitoneal injection of a mixture containing chloralose 80 mg/kg and sodium pentobarbitone 6 mg/kg. The trachea was cannulated and systemic arterial pressure was monitored from a cannulated common carotid artery by means of a Statham (Model P23AC) pressure transducer. Heart rate was recorded in all the cats by means of a Grass (model 7P4C) tachograph triggered by the systemic arterial pressure. The cats were bilaterally vagotomized. All records were made on a 6-channel Grass Curvilinear polygraph (model7). In all experiments, drugs were injected through a cannula in a femoral or brachial vein.

Pulmonary Artery Pressure

The thorax was opened by making a slit through the chest wall at the level of the second or third intercostal space. The heart was shelled from its pericardium and, to measure pulmonary artery pressure, a 13_g hypodermic needle, attached via a short length of a polythene cannula to a Statham (model P23AC) pressure transducer, was injected into the pulmonary artery at its point of origin from the right ventricle.

Pulmonary resistance and compliance

The method used was based on the concept first described by Neergard & Wirz (12) and later modified by Mead & Whittenberger (13), Amdur & Mead (14), Colebatch, Olsen & Nadel (15) and Diamond (16, 17).

The cats were artificially ventilated by positive pressure at a frequency of 27-20 breaths per minute, and a stroke volume of 13 ml/kg body weight using a Palmer Ideal pump. Airflow was measured using a pneumotachograph (Mercury Electronics F2-12mm) coupled to a Statham differential pressure transducer (model PM 5). Transpulmonary pressure was measured by connecting one inlet port of a Statham differential pressure transducer (model PM 5) to a 13_g hypodermic needle which was inserted into the side arm of the tracheal tube by means of a polythene tube. Since the chest was open the intrathoracic pressure was considered to be atmospheric.

Tidal volume was obtained from the electronic integration of the flow signal by a Grass (model 7P10) integrator. All three parameters, that is, transpulmonary pressure, rate of airflow and tidal volume, were recorded simultaneously.

Method of Analysis

Pulmonary resistance was calculated from the airflow and transpulmonary pressure records at isovolumic points on the tidal volume trace as described by Amdur & Mead (14). The calculation was based on the airflow and the component of the transpulmonary pressure required to overcome flow resistance near peak inspiratory and expiratory flow rates.

The calculation of pulmonary compliance was also based on the method of Amdur and Mead (14). In this instance, it is assumed that at the beginning and end of inspiration, no air is being moved either into or out of the respiratory system and under static conditions the flow-resistive forces are inoperative; any change in transpulmonary pressure, therefore must relate to the elastic forces alone.

Procedure

Cumulative doses of 5-hydroxytryptamine were injected through the brochial vein and the effect was noted on the systemic arterial blood pressure, heart rate, diastolic pulmonary artery pressure, transpulmonary pressure, airflow and tidal volume. The injection was continued until about 5-8 mmHg increase in diastolic pulmonary artery pressure was obtained. Maximum increase in diastolic pulmonary artery pressure was not possible as this would cause occlusion of blood to the lungs, alveolar collapse and eventual death of the animal. Next, isoprenaline (a non-selective B_1, B_2- adrenoceptor agonist) was infused through the femoral vein at the rate of 0.5 ug/kg/min and, at a stable heart rate, cumulative doses of 5-hydroxytryptamine were injected. Both isoprenaline infusion and 5-hydroxytryptamine administration were stopped when about 5-8 mmHg increase in diastolic pulmonary artery pressure was obtained. Rimiterol (a selective B_2-adrenoceptor agonist) infusion at the rate of 0.25ug/kg/min was made in place of isoprenaline and the 5-hydroxytryptamine doses were again injected cumulatively. The doses of isoprenaline and rimiterol were chosen after several trials to determine suitable doses that could antagonise the effects of 5-hydroxytryptamine on all parameters. An interval of about one hour was allowed between successive procedures to enable the various parameters to recover fully from the effects of 5-hydroxytryptamine.

Practolol (a selective B_1- adrenoceptor antagonist) 0.5 mg/kg was injected, followed, after ten minutes, by the isoprenaline infusion and 5-hydroxytryptamine injection. Rimiterol was also used in place of isoprenaline. In a similar way, the effect of butoxamine (a selective B_2-adrenoceptor antagonist) 5 mg/kg was investigated on the isoprenaline and rimiterol infusions during the injection of 5-hydroxytryptamine administered cumulatively.

Cumulative dose-response curves to histamine and noradrenaline were also obtained on the systemic arterial pressure, heart rate, pulmonary artery pressure, transpulmonary press, airflow and tidal volume. The effect of propranolol 1.5 mg/kg was also observed on all parameters.

Unless otherwise stated the drug doses in these experiments refer to the bases. Stock solutions in all experiments were freshly prepared in 0.9%w/v acid saline (pH-4.0) and diluted with normal saline.

Result

Typical effect of 5-hydroxytryptamine on the various parameters are shown in *Fig.*1. (See page 15)

Diastolic Pulmonary Artery Pressure and Pulmonary Resistance and Compliance

5-hydroxytryptamine caused an increase in diastolic pulmonary pressure, pulmonary pressure and a decrease in pulmonary compliance. Dose-dependent curves were obtained for diastolic pulmonary artery pressure, and pulmonary resistance and compliance. *Fig.* 2 shows the dose-response curves to 5-hydroxytryptamine on the cast diastolic pulmonary artery pressure in the presence of isoprenaline, rimiterol and practolol. Similar curves to the same agent and relaxants in the presence of butoxamine were also obtained. Whereas the effect of isoprenaline was consistent in both cases in that the drug produced a rightward shift of the 5-hydroxytryptamine curve in one case (*Fig*. 2) and a leftward shift in the other. The effects of isoprenaline and rimiterol on the diastolic pulmonary artery pressure were not diminished by practolol (*Fig*.2) but the effect of isoprenaline on this parameter was reversed by butoxamine.

Isoprenaline and rimiterol antagonized the effect of 5-hydroxytryptamine on the cat pulmonary resistance and practolol had very little, if any, effect on this antagonistic action. On the other hand,butoxamine reversed similar effects by isoprenaline and rimiterol on 5-hydroxytryptamine.

Isoprenaline and rimiterol antagonized the effects of 5-hydroxytryptamine on pulmonary compliance and practolol had practically no effect on this antagonist action. However, butoxamine reversed similar effects of isoprenaline and rimiterol on 5-hydroxytryptamine.

Butoxamine showed a greater antagonistic action against isoprenaline than rimiterol on the cat diastolic pulmonary artery pressure and pulmonary compliance and resistance.

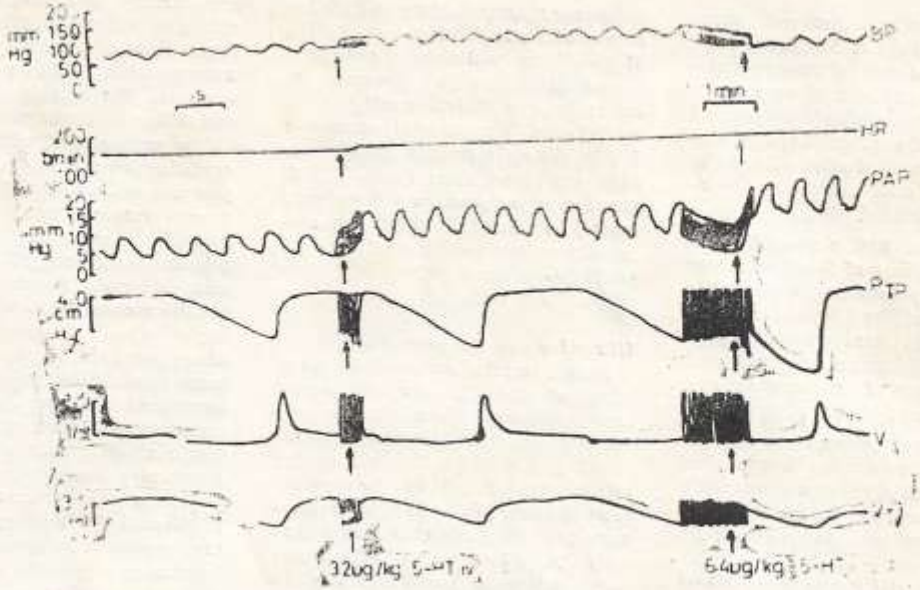
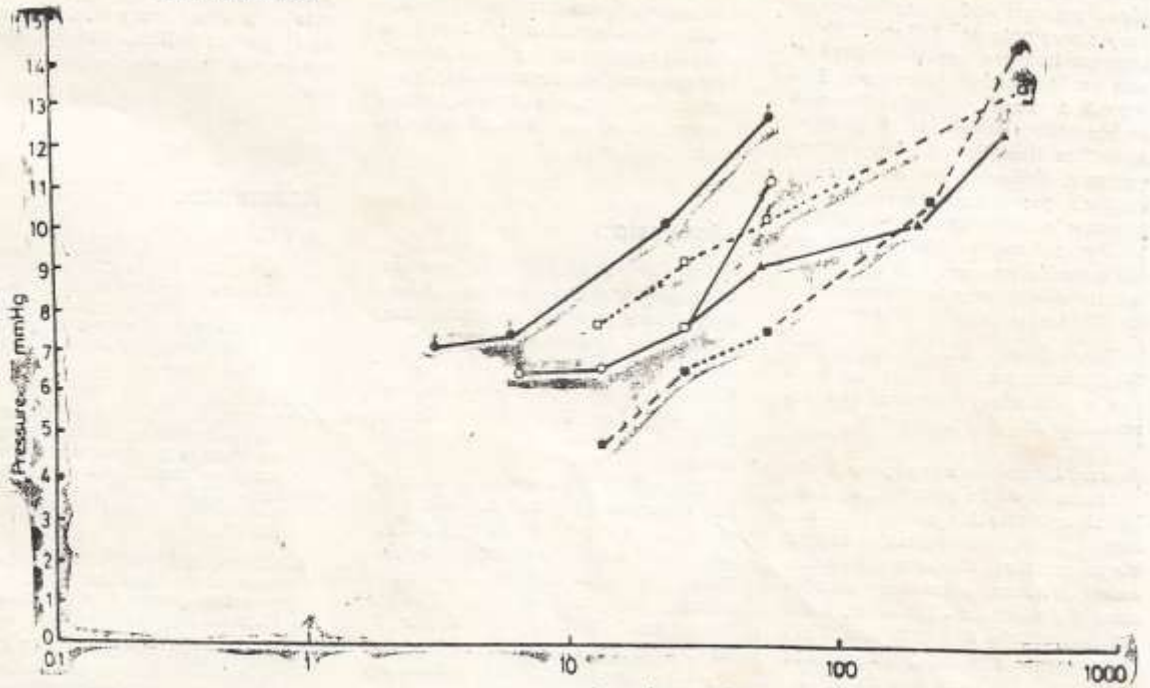


Fig. 1 The effects of 5-Hydroxytryptamine (5HT) injected intravenously on, reading from the top downwards, blood pressure (BP) heart rate (HR), Pulmonary Artery Pressure (PAP), Transpulmonary Pressure (PTP), airflow (V) and tidal volume (VI). In this experiment, the cat was bilaterally vagotomised. The chart speed was increased at two points; the first during the control period and the second at the height of the 5-HT effect. 5-HT produced a rise in pulmonary arterial pressure and heart rate. Transpulmonary pressure was increased whilst airflow decreased. Tidal volume was relatively unaffeted.



16 CUMULATIVE DOSE-RESPONSE CURVES TO 5-HYDROXYTRYPTAMINE (●) ON THE DIASTOLIC PULMONARY ARTERY PRESSURE IN THE PRESENCE OF ISOPRENALINE (■) RIMITEROL (○) ISOPRENALINE + PRACTOLOL (▲) AND RIMITEROL + PRACTOLOL (□)

Systemic Arterial Pressure and Heart Rate

All the above changes were accompanied by changes in the systemic blood pressure and heart rate. 5-hydroxytryptamine produced an initial decrease in systemic blood pressure and diastolic pulmonary artery pressure followed by an increase in these parameters. There was an in heart rate. Isoprenaline caused an initial decrease in systemic arterial blood pressure as well as diastolic pulmonary artery pressure followed by an increase in both parameters; there was an increase in heart rate. Rimiterol had similar action as isoprenaline on the systemic pressure and heart rate but the effects were less pronounced in the former case.

Throughout the experiments, 5-hydroxytryptamine produced a rise in pulmonary resistance and isoprenaline and rimiterol a fall.

Practolol, butoxamine and propranolol

Practolol on its own has a slight initial bradycardiac action but had little effect on the systemic arterial blood pressure, diastolic pulmonary artery pressure, pulmonary compliance and resistance. However, butoxamine, after a slight, transient fall in systemic arterial pressure and heart rate, produced a considerable increase in the former; there was little change in heart rate. On the average, butoxamine produced a rise of about 1.3 mmHg in diastolic pulmonary artery pressure, an increase of about 25cm.

H_2^{01}-^1_s-^{1} in pulmonary resistance accompanied by a decrease of approximately 2.3ml cm $H_2^{0\text{-}1}$ in compliance. Propranolol caused a fall in systemic arterial blood pressure and heart rate; diastolic pulmonary artery pressure was reduced from 5 5o 3mmHg, pulmonary resistance was increased from 3.8 to 4.1 cm H_2^{01}-^1_s-^{1} and pulmonary compliance was little affected.

Histamine and Noradrenaline

Both histamine and noradrenaline increased the diastolic pulmonary artery pressure. Noradrenaline was more potent than histamine in increasing the diastolic pulmonary artery pressure but was less potent than the latter in increasing pulmonary compliance. Noradrenaline had only little effect on the cat pulmonary resistance and much less so in decreasing pulmonary action on pulmonary compliance was negligible. Histamine generally produced a decrease in systemic arterial pressure, followed by a slight increase and then a decrease again; heart rate was little affected. Noradrenaline produced a considerable increase in Systemic arterial pressure but correspondingly less increase in diastolic pulmonary artery pressure, there was also a slight increase in heart rate.

Discussion

The effect of both isoprenaline and rimiterol on diastolic pulmonary artery pressure, on pulmonary compliance and on pulmonary resistance were unaffected by cardio-selective doses of practolol, suggesting that B_1- adrenoceptors are not involved in mediating any of these effects.

The effects of isoprenaline on all three parameters, and the effects of rimiterol on pulmonary compliance and resistance were blocked by butoxamine indicating that all these effects were mediated by B^2 –adrenoceptors in the pulmonary arterioles of man which mediate vasoconstriction and vasodilation respectively. However the effect of butoxamine on the

diastolic pulmonary artery pressure response to rimiterol was not blocked, and the interactions of rimiterol and 5-hydroxytryptamine on this parameter was variable. No explanation of this variability is apparent.

The pronounced effects of noradrenaline on systemic arterial blood pressure on diastolic pulmonary artery pressure contrasted with its negligible effect on pulmonary compliance. Since drug effects on systemic arterial blood pressure are usually accompanied by corresponding changes in diastolic pulmonary artery pressure, changes in the systemic circulation may be another complicating factor in attempts to correlate the effects of alteration in diastolic pulmonary pressure on pulmonary compliance. It is difficult to reconcile the pronounced increase in diastolic pulmonary artery pressure produced by noradrenaline with its almost negligible effect on pulmonary compliance. In conclusion, the results suggest that while changes in pulmonary compliance may be secondary to changes in pulmonary artery pressure with some drugs (e.g. isoprenaline), as yet undetermined, other factors may play a role with other drugs (e.g. rimiterol and noradrenaline). These other actors will be the subject of further studies

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