ADRENERGIC RECEPTIVE MECHANISM IN THE PULMONARY CIRCULATION IN DOGS*

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The pulmonary circulatory changes caused by adrenergic drugs using several techniques have been demonstrated by many investigators. The pulmonary arterial pressure and the pulmonary resistance increase with epinephrine, levarterenol and phenylephrine (1-4). Isoproterenol reduces the pulmonary arterial pressure (5, 6). Methoxamine causes either no change in pulmonary arterial pressure (7) or a significant pulmonary hypotension (4, 8).

On the other hand, the idea of an adrenergic receptive mechanism was introduced by Langley (9, 10) and the receptor concept was reported by Dale (11) describing two kinds of receptors in the general circulation: receptors having an action resulting in excitation and receptors having an action resulting inhibition of the effector cells. But these two kinds of receptors do not exist in all the places of the body both together, sometimes, only one kind of receptor can be found in some places. We have classified the adrenergic receptors in several organs of the body using several adrenergic drugs and the adrenergic blocking agents (12-16).

We have attempted to demonstrate in this paper the kind of adrenergic receptor existing in the pulmonary circulation since no references exist on this problem, even though many investigators have observed the action of adrenergic drugs in the pulmonary circulation, using a limited lung circulation technique and maintaining as normal a circulation as possible.

METHODS

Fifty-two dogs of either sex were anesthetized with intravenous injection of pentobarbital sodium, 15 mg/kg, about 30 minutes after a subcutaneous injection of morphine sulfate, 10 mg/kg. Atropine, 1 mg/kg, was injected with the morphine. Heparin sodium, 1000 U.S.P. units, was used as the anticoagulant.

Fig. 1 shows the partial lung circulation technique used in these experiments. The left chest was widely opened under artificial positive pressure respiration. The upper

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FIG. 1. The schema of partial lung circulation technique. Left lower lobe. AR—Artificial respiration through the tracheal cannula. LPA—Left pulmonary artery. PV—Pulmonary vein. LA—Left atrium. F—Flowmeter. FA—Femoral artery. R—Reservoir. I—Injection. PAP—Pulmonary arterial pressure. SAP—Systemic arterial pressure. PVF—Pulmonary vein outflow.

(Apical) and middle (Cardiac) lobes off the left lungs were cut off with ligation of the correspondent pulmonary arteries, bronchi and veins, leaving only the lower (Diaphragmatic) lobe remaining after this operation.

A Statham pressure transducer was connected with a catheter introduced into one of the cut lobar branches of the pulmonary artery in order to measure the pulmonary arterial pressure. A small catheter was introduced into the other cut lobar branch of the pulmonary artery in order to inject drugs. However, in a few cases, there is only one branch of the pulmonary artery for both these lobes, in these cases, both catheters were introduced into this branch. The pulmonary veins of the left lower lobe were cannulated with a small Y vinyl tube in order to realize a long bypass from the left pulmonary veins to the left atrium (the volume of this bypass was about 25–35 c.c.).

Thus, from the left lower lobe, the blood flows through the bypass and back to the left atrium. A cannulating type of electromagnetic flowmeter (F) was placed in this bypass close to the pulmonary veins in order to measure continuously the pulmonary vein outflow. The pulmonary vein outflow from the left lower lobe in these experiments, in normal condition, was 80–210 c.c./min. Blood was infused from a reservoir (R), in case of a bleeding during or after the operation. The right lung was left undisturbed.

The systemic arterial pressure was recorded by Statham transducer from the femoral artery. The heart rate was counted from the arterial pressure pulse records.

In some cases, adrenergic drugs were injected into the ascending aorta just distal

to the aortic valve or into the left ventricle through a small catheter inserted from the left common carotid artery. Those injections were made in order to compare the effect on the pulmonary arterial pressure and the pulmonary vein outflow between the injections made in the pulmonary circulation or the general circulation. The position of the catheter for aortic or left ventricular injections was checked by the pulse contour on the record of the Statham transducer.

The following adrenergic drugs were used; epinephrine chloride (0.01–0.1%) as *alpha-beta* type, levarterenol bitartrate (0.01–0.1%) and phenylephrine hydrochloride (0.1–1%) as *alpha* type, isoproterenol hydrochloride (0.02%), ethylnorepinephrine hydrochloride (Butanefrine) (0.1–1%) as *beta* type adrenergic drug. Phenoxybenzamine (Dibenzylamine), 5 mg/kg, 1,4-bis(benzodioxane-2-yl-methyl) piperazine (Dibozane), 1 mg/kg, were used as *alpha* type adrenergic blocking agents and *beta*-hydroxy-N-isopropyl-3,4 dichlorophenethylamine (dichloro-isoproterenol, DCI) 1–4 mg/kg for *beta* blockade. All drugs were diluted in 0.9% sodium chloride solution. Blocking agents were diluted in 5–10 c.c. volume of 0.9% sodium chloride solution and infused slowly into the left pulmonary artery.

RESULTS

Comparison of the effects between pulmonary arterial and aortic injections of epinephrine

Fig. 2 shows, on the left, the effects of epinephrine (10 μ g/kg) injected into the pulmonary artery of the left perfused lobe and, on the right, the result of an injection into the aorta just distal to the aortic valve.

When epinephrine 10 μ g/kg was injected into the perfused lobe, the pulmonary arterial pressure began to increase immediately after the injection, this increase (1st

FIG. 2. The pulmonary arterial pressure, systemic arterial pressure and pulmonary vein outflow changes produced by epinephrine (10 μ g/kg) injected into the pulmonary circulation (A) and into the aorta just distal to the aortic valve (B). From top to bottom: pulmonary arterial pressure (PAP), systemic arterial pressure (SAP) and pulmonary vein outflow (PVF). Numbers on the record are heart rate. At signal mark, epinephrine, 10 μ g/kg, was injected.

change) lasting about 15–30 seconds, depending only upon the flow of the perfused lobe, because the drug does not reach the left ventricle and the systemic circulation before passing through the bypass. At the same time, the pulmonary vein outflow decreased and the pulmonary resistance increased corresponding to the time where the drug is in the pulmonary circulation. The systemic arterial pressure started to increase about 10–15 seconds or more after the injection of the drug. However, at this time, the pulmonary arterial pressure was already higher than the control level. In one-third of the experiments, the pulmonary arterial pressure curve showed a peak before any change in the systemic arterial pressure with the heart rate being unchanged during this period.

When, the drug reached the systemic circulation, the pulmonary arterial pressure increased again (2nd change), the latter change being much higher than that of 1st one, and the pulmonary vein outflow increased. The systemic arterial pressure increased much higher than previously and the heart rate also increased.

On the other hand, after the injection of epinephrine $10\text{ }\mu\text{g/kg}$ into the aorta or into the left ventricle, the systemic arterial pressure increased first immediately after the injection of drug, and the pulmonary arterial pressure increased later at about 5–10 seconds after the change of the systemic arterial pressure and at the same time, the heart rate and the pulmonary vein outflow increased. Sometimes, the pulmonary arterial pressure decreased slightly just after the increasing of the systemic arterial pressure and then went up much higher than its control level. The pulmonary arterial pressure did never increase before the change of the systemic arterial pressure, when the drug was injected into the aorta or into the left ventricle.

Furthermore, the level of the systemic arterial pressure corresponding to the peak of the 1st change of the pulmonary arterial pressure was much lower when the drug was injected into the perfused lobe than the systemic arterial pressure corresponding to the beginning of the pulmonary arterial pressure increase when the drug was injected into the aorta.

The changes of the pulmonary arterial pressure, pulmonary vein outflow, systemic arterial pressure and heart rate after the injection of epinephrine into the aorta or into the left ventricle were practically the same as the 2nd changes caused by the injection of epinephrine into the left perfused lobe.

From these experiments, we assume that the 1st change of the pulmonary arterial pressure and the pulmonary vein outflow following the epinephrine injected into the left perfused lobe is due to a primary pulmonary vasoconstriction to the drug itself and is not due to a secondary effect following the systemic arterial pressure change, as there is no relationship between the 1st pulmonary arterial pressure change and the systemic arterial pressure change.

Our main purpose in these experiments was to investigate the 1st change of the pulmonary arterial pressure and pulmonary vein outflow while the drug, injected into the partial lung, is in the pulmonary circulation,

Effects of several drugs

Epinephrine: When epinephrine 1–3 $\mu\text{g/kg}$ was injected into the perfused lung, the pulmonary arterial pressure increased 3.5–4% and the pulmonary resistance also increased about 5.5–8% at the peak of the 1st change of the pulmonary arterial pressure. However, in some cases, there was no significant change of the pulmonary arterial pressure and the pulmonary resistance while the drug is in the pulmonary circulation. After the injection of epinephrine (10–15 $\mu\text{g/kg}$) into the pulmonary circulation, the pulmonary arterial pressure increased about 8–16% and the pulmonary resistance increased about 15–24%. All these changes were significant. The same amount of epinephrine was injected into the perfused lobe after an injection of DCI (1–4 mg/kg) into the pulmonary artery. The pulmonary arterial pressure and the pulmonary resistance changes were almost the same as the control response as shown in Fig. 3B. However, the pulmonary arterial pressure and the pulmonary resistance changes caused by epinephrine were completely blocked or markedly reduced after a perfusion of dibozane (1 mg/kg) or dibenzyliline (5 mg/kg) into the pulmonary artery as shown in Fig. 3C.

FIG. 3. The pulmonary arterial pressure, systemic arterial pressure and pulmonary vein outflow changes by epinephrine (10 $\mu\text{g/kg}$) injected into the pulmonary circulation. A—Control. B—After DCI 1 mg/kg. C—After dibozane 1 mg/kg. Curves as in Fig. 2.

The second change of the pulmonary arterial pressure while the epinephrine reaches the systemic circulation was also blocked or markedly reduced after dibozane or dibenzyliline. The systemic arterial pressure response to epinephrine was blocked or markedly reduced after dibozane or dibenzyliline. In some of the experiments, the systemic arterial pressure decreased after dibozane or dibenzyliline (Epinephrine reversal) as shown in Fig. 3C. However, no “Epinephrine reversal” on the pulmonary arterial pressure could be observed while the drug is in the pulmonary circulation.

Levarterenol: One to 15 $\mu\text{g/kg}$ of levarterenol were injected into the pulmonary circulation. The pulmonary arterial pressure and the pulmonary resistance changes were very similar to the responses to epinephrine. After DCI (1–4 mg/kg) the effect of levarterenol injected into the pulmonary circulation was comparable to the control. There was no significant difference between control response and the response after DCI. However, when dibozane (1 mg/kg) or dibenzyliline (5 mg/kg) was infused into

the pulmonary circulation, no pulmonary arterial pressure change was recorded or the change was very slight if a high dose of levarterenol was used. A similar response of the pulmonary resistance to levarterenol after dibozane or dibenzyline was observed.

The second change of the pulmonary arterial pressure and the systemic arterial pressure after the arrival of the drug into the systemic circulation was similar to the control response even after DCI. The pulmonary vein outflow was increased when levarterenol reaches the systemic circulation and this response was not prevented by DCI.

The second change of the pulmonary arterial pressure and the effect on the systemic arterial pressure caused by levarterenol were completely blocked or markedly reduced by dibozane or dibenzyline and almost no change of the pulmonary resistance was recorded after these drugs.

Phenylephrine: The pulmonary arterial pressure increased and the pulmonary vein outflow decreased with phenylephrine 10–150 $\mu\text{g/kg}$ while the drug was in the pulmonary circulation. After DCI (1–4 mg/kg) these responses were similar to the control response while the effect of phenylephrine on the pulmonary arterial pressure and on the pulmonary vein outflow was almost completely blocked by dibozane or dibenzyline.

When phenylephrine reaches the systemic circulation, the pulmonary arterial pressure and the systemic arterial pressure increased much more than that during the period while the drug is only in the pulmonary circulation. However, the pulmonary vein outflow and the heart rate were almost unchanged. After dibozane or dibenzyline these changes in the pulmonary arterial pressure and the systemic arterial pressure were almost completely blocked.

Isoproterenol: After the injection of isoproterenol (1–15 $\mu\text{g/kg}$) into the pulmonary circulation, the pulmonary arterial pressure and the pulmonary vein outflow were practically unchanged while the drug was in the pulmonary circulation. After blocking agents, there was no significant difference from the control response.

When isoproterenol went into the systemic circulation, the pulmonary arterial pressure increased slightly, the heart rate markedly increased and the pulmonary vein outflow slightly increased while the systemic arterial pressure decreased. However, if the systemic arterial pressure decreased markedly, at the same time, the pulmonary arterial pressure slightly decreased.

After dibozane or dibenzyline, the response to isoproterenol reaching the systemic circulation was similar to the control. But when isoproterenol was injected after DCI, the systemic arterial hypotension was reduced and sometimes, completely blocked by DCI in high dose. However, there was no marked difference between the pulmonary arterial pressure and the pulmonary vein outflow changes and the control response.

Ethylnorepinephrine: Ethylnorepinephrine (10–150 $\mu\text{g/kg}$) was injected into the pulmonary circulation. The pulmonary arterial pressure and the pulmonary resistance were practically not affected by the drug in the pulmonary circulation. The response was the same even after injection of blocking agents.

When the drug went into the systemic circulation, the systemic arterial pressure decreased and the pulmonary arterial pressure increased or slightly decreased. The pulmonary vein outflow and the heart rate were almost unchanged.

The systemic arterial pressure increased after DCI while the pulmonary arterial pressure, pulmonary vein outflow and heart rate were comparable to the control. After dibozane or dibenzyline, the systemic arterial pressure, pulmonary arterial pressure, pulmonary vein outflow and heart rate were almost similar to the control response.

Fig. 4 shows the percentage of change of the pulmonary arterial pressure and the pulmonary resistance caused by the several drugs while they are in the pulmonary circulation in control, after DCI and after dibozane or dibenzyline.

FIG. 4. The percentage change in pulmonary arterial pressure (upper curves) and the pulmonary resistance (lower curves) caused by several drugs while they are in the pulmonary circulation in control (left), after DCI (middle) and after dibozane or dibenzyline (right).

DISCUSSION

Daly (1), Hebb and Konzett (6), Edwards (2), Rose *et al.* (3), Aviado *et al.* (4) etc. using the lung perfusion technique described epinephrine as producing a local vaso-

constriction in the pulmonary circulation in dogs.

In our experiments, we agree that a pulmonary hypertension is induced by epinephrine as well as a decrease of the pulmonary vein outflow. We used the partial lung perfusion technique on atropinized dogs in order to avoid any cholinergic effect.

On the other hand, epinephrine is well known as a *alpha-beta* type adrenergic drug which produces the systemic vasoconstriction and a systemic vasodilatation (Epinephrine reversal) when injected after *alpha* type adrenergic blocking agents such as dibozane.

In our experiments, epinephrine produces an hypertension in the pulmonary artery and it can not be altered by *beta* type blocking agents such as DCI while it can be blocked by *alpha* type blocking agents such as dibozane. But "Epinephrine reversal" could not be observed in the pulmonary circulation as in the systemic circulation.

From these results obtained with epinephrine, it is obvious that adrenergic receptor of *alpha* type are present in the pulmonary circulation while the existence of *beta* type receptors is doubtful.

The pulmonary hypertension caused by another *alpha* type adrenergic drugs such as levarterenol and phenylephrine was observed and this hypertension could be blocked by *alpha* type blocking agents such as dibozane or dibenzylinc. This observations confirm the evidence of *alpha* type adrenergic receptors in the pulmonary circulation.

Furthermore, the pulmonary arterial pressure and the pulmonary vein outflow are almost unchanged by the injection into the pulmonary circulation of isoproterenol or ethylnorepinephrine which are *beta* type adrenergic drugs, even after *alpha* and *beta* type adrenergic blocking agents such as dibozane, dibenzylinc and DCI.

From these observations we assume that the pulmonary circulation is provided with only *alpha* adrenergic receptors.

SUMMARY

The pulmonary circulatory changes caused by several adrenergic drugs were observed with partial lung circulation technique in atropinized dogs.

An increase of the pulmonary arterial pressure accompanied by a decrease of the pulmonary vein outflow and the calculated pulmonary resistance were recorded with epinephrine, levarterenol and phenylephrine. These effects were abolished or markedly reduced by dibozane and dibenzylinc. No "Epinephrine reversal" was observed in the pulmonary circulation with epinephrine after dibozane or dibenzylinc.

Isoproterenol and ethylnorepinephrine have no effect on the pulmonary circulation of the atropinized dogs in these experiments.

From these results, we assume that the pulmonary circulation is provided of *alpha* type adrenergic receptors but of no *beta* receptors.

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