Br. J. Pharmac. (1970), **38**, 374–385.

Pharmacological significance of biogenic amines in the lungs: noradrenaline and dopamine

DOMINGO M. AVIADO AND CHIRAVAT SADAVONGVIVAD*

Department of Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Summary

1. The noradrenaline concentration in the lung was less than 0·5 μg/g in eight animal species.

2. In the cat, dog, rabbit and goat, tyramine produced a fall in pulmonary resistance, which was reduced by the administration of either reserpine or cocaine. Although an infusion of noradrenaline increased the content of this amine in the lung of the cat, previously depleted by reserpine, the bronchodilator property of tyramine was not restored. The infusion of isoprenaline did not restore the response to tyramine. The role of either catecholamine in mediating the bronchomotor response to tyramine could not be ascertained.

3. The concentration of dopamine was as high as 6·4 μg/g in the goat lung and less than 0·5 μg/g in the lungs of the cat, rabbit, dog, rat, mouse, guinea-pig and man. Dopamine, injected intravenously into the cat, dog, rabbit and goat, produced a slight rise in pulmonary resistance. This increase was blocked by tolazoline, indicating that the response was mediated by α-adrenoceptors in the bronchial passages. No procedure has been observed to influence the dopamine content of the lung. The release of dopamine cannot, however, be excluded until the blood in the bronchial veins has been analysed.

Introduction

There are several inconsistencies in regard to the pharmacological significance of catecholamines in the tracheobronchial system. Although the bronchodilator properties of adrenaline and isoprenaline are certain, the nature of the bronchomotor effect of noradrenaline is not clear. In the isolated tracheal preparation, noradrenaline is a weaker relaxant than the other two amines (Daly & Hebb, 1966). In the intact lung, there is a reduction in pulmonary resistance, but it is difficult to distinguish between a true relaxation of bronchial muscles and the shrinking of bronchial mucosa caused by noradrenaline. In some preparations an increase in pulmonary resistance has been demonstrated which appears to be mediated by α-adrenoceptors in the airways (Castro de la Mata, Penna & Aviado, 1962). It has therefore been difficult to accept noradrenaline as the neurohumoral mediator for the sympathetic bronchodilator nerves.

The effects of reserpine and tyramine on the airways are completely unknown. In the cardiovascular system, the ability of tyramine to release noradrenaline from

* Formerly Predoctoral Fellow of the Rockefeller Foundation. Present address: Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand.

stores that can be depleted by reserpine has been widely accepted (Muscholl, 1966). In the bronchopulmonary system, a reduction in the content of catecholamine in the lung, induced by reserpine, has been incidentally reported by Paasonen & Krayer (1958). The functional consequences of this reduction have not been investigated by testing the effect of tyramine on the lung of an animal that has been pretreated with reserpine.

Although the content of dopamine in the lung is low in most animal species, its content in the lung of ruminants is high (Euler & Lishajko, 1957 ; Bertler & Rosengren, 1959). The function of dopamine in the lung has not been settled. The bronchomotor effects of dopamine in the dog have been reported to be unimportant, but no information is available on its bronchomotor effect in the ruminants.

This paper is concerned with noradrenaline and dopamine in the lung. The bronchomotor effects and content of both catecholamines are correlated in the lungs of four animal species: the rabbit, cat, dog and goat. The effects of reserpine, dopamine and tyramine were investigated by the use of supplementary agents such as cocaine, tolazoline, noradrenaline, isoproterenol and sotalol (±-4(2-isopropylamino-1-hydroxyethyl)methanesulphonanilide HCl). The last-mentioned compound is a blocker of β-adrenoceptors (Folle & Aviado, 1965), and is also known as MJ 1999. No attempt has been made to identify the neurohumoral transmitter involved in sympathetically induced bronchodilatation. Additional evidence has become available, indicating that the transmitter may be a substance other than noradrenaline or isoprenaline.

Methods

Procedures in the rabbit

The initial study involved two groups: one group of nine rabbits and a second group of six rabbits. The animals in the latter group received an injection of reserpine (5 mg/kg) intraperitoneally, 24 hr before killing. For the removal of the lung, the rabbit was anaesthetized with diallylbarbituric acid (60 mg/kg) and urethane (240 mg/kg) intravenously, the animal was decapitated and the lungs were removed. The method for analysis of the lung was described by Sadavongvivad (1970).

Five rabbits were anaesthetized as in the first study. The femoral artery was catheterized for the measurement of aortic pressure. The trachea was cannulated and pulmonary resistance and compliance were measured by the technique described by Klide & Aviado (1967). These rabbits were also used to study the effects of intravenous injections of dopamine (10 μg/kg) and tyramine (2 mg/kg). In three of the five rabbits, tolazoline (4 mg/kg) was injected and the injections of the amines were repeated.

Procedures in the cat

Cats of both sexes, weighing 2 to 4 kg, were anaesthetized with chloralose (100 mg/kg) administered intraperitoneally. The trachea, femoral artery and vein were cannulated. The cat was prepared for measurement of pulmonary resistance and compliance. The chest was opened at the midline, and the lung samples were

removed by ligating and excising pieces of lung tissue, when required. The following series of experiments were completed:

Reserpine treatment. One group, consisting of eight cats, did not receive any premedication. Ten cats received reserpine (3 mg/kg) injected intraperitoneally 24 hr before the experiment. During the experiment, tyramine and cocaine were injected intravenously in a total volume of 0·2 to 0·5 ml. Noradrenaline and isoprenaline were administered as an intravenous infusion. A continuous infusion pump was used to deliver the drug solutions at a rate of 0·2 ml/min for 20 min. The noradrenaline and isoprenaline solutions were used at a concentration of 125 μg/ml in 0·9% sodium chloride solution. Samples of lung tissue were removed at the start of each experiment and at various times after the injection of the various drugs.

A further group consisting of five cats did not receive any premedication. They were anaesthetized with chloralose (100 mg/kg) and prepared for recording pulmonary resistance, compliance and aortic blood pressure. The following drugs were injected intravenously: tyramine (0·1 to 0·4 mg/kg), dopamine (10 μg/kg), tolazoline (4 mg/kg) and sotalol (2 mg/kg).

Procedures in the dog

Dogs of both sexes, weighing 6 to 10 kg, were anaesthetized by intravenous injection of chloralose (100 mg/kg) 1 hr after a subcutaneous injection of morphine sulphate (2 mg/kg). Pulmonary compliance and resistance were measured. Lung samples were removed from the animal with the chest opened in the midline, as described for the cat.

One group, consisting of five dogs, received no premedication, while a second group, consisting of three dogs, received an injection of reserpine (3 mg/kg) subcutaneously 18 to 24 hr before the experiment. After anaesthesia was induced with chloralose, the chest was opened and a lung sample was removed for chemical analysis. Dopamine (10 μg/kg), tolazoline (4 mg/kg) and sotalol (2 mg/kg) were injected intravenously.

A further group of eight dogs did not receive any premedication. They were used to determine the nature of the responses to the intravenous injection of tyramine (0·2 mg/kg) and dopamine (10 μg/kg).

Procedures in the goat

Seven goats, weighing 16 to 31 kg, were anaesthetized by an intravenous injection of sodium pentobarbitone 25 mg/kg. It was found that the effect of pentobarbitone wore off rapidly, so that additional doses (total 60 mg) had to be administered intermittently. The following procedures were carried out: cannulation of the trachea ; cannulation of one femoral vein for the injection of the drugs ; cannulation of both femoral arteries for the measurement of the aortic blood pressure and withdrawal of the blood samples ; the chest was opened at the third intercostal space on the left side and a polyethylene catheter was inserted into the pulmonary artery through an incision in the right atrium to enable the measurement of the pulmonary arterial pressure. The animal was maintained on a respiratory pump at the rate of 24 breaths per min and a constant tidal volume of between 150 and 250 ml,

depending on the size of the goat. Pulmonary compliance and resistance were measured by the method used in the three other animal species.

The goats were divided into two groups: a group of five goats receiving no premedication, and a group of three goats that were given reserpine (2 to 4 mg/kg) 18 hr before the experiment. Dopamine (1, 10 or 100 μg/kg) was injected through a catheter in a femoral vein. After each injection, changes in pulmonary compliance and resistance were recorded at intervals for 5 min.

Chemical analysis of the human lung

Samples were obtained from human lung at surgery or at autopsy. The samples were analysed for biogenic amines by the same method as that used for the lungs of the other animal species.

Results

Content of biogenic amines

The results of the analysis of the lung obtained from five species are summarized in Table 1.

The mean concentrations of noradrenaline in the lungs of the five species investigated were below 0·5 μg/g. The mean concentrations of dopamine were 0·1 μg/g or lower except in the goat lung, which had a mean value of 6·4 μg/g. These values for biogenic amines are in general agreement with those reported in the literature.

Effect of reserpine

The effect of reserpine, administered 18 to 24 hr before killing the animal, on the concentrations of the biogenic amines in the lungs of four species is illustrated in Table 1. In all four species (cat, rabbit, dog and goat) there was no change in the concentrations of histamine and dopamine and a reduction in the concentrations of 5-HT after reserpine. A reduction in noradrenaline after reserpine was observed in the cat and dog but not in the rabbit and goat. The amount of reserpine administered was sufficient to sedate all the animals, so that the difference in effect between species cannot be accounted for by an insufficient dose.

TABLE 1. *Influence of reserpine on content of biogenic amines in the lung of five species*

Species	Procedure and No. of animals	Mean ± S.E.M. (μg/g lung)			
		Histamine	5-HT	Noradrenaline	Dopamine
Cat	Control (8)	12·03 ± 2·27	3·22 ± 0·48	0·47 ± 0·08	0·11 ± 0·02
	Reserpine (10) (3 mg/kg i.p.)	12·14 ± 1·80	1·54* ± 0·18	0·06* ± 0·02	0·10 ± 0·01
Rabbit	Control (9)	4·86 ± 1·08	7·34 ± 1·66	0·08 ± 0·02	0·05 ± 0·02
	Reserpine (6) (5 mg/kg i.p.)	3·22 ± 1·16	0·50* ± 0·23	0·06 ± 0·04	0·05 ± 0·02
Dog	Control (5)	27·71 ± 4·50	0·53 ± 0·10	0·35 ± 0·02	0·06 ± 0·02
	Reserpine (3) (3 mg/kg i.p.)	31·28 ± 6·47	0·14* ± 0·03	0·12* ± 0·04	0·05 ± 0·01
Goat	Control (5)	38·44 ± 5·72	3·69 ± 0·47	0·29 ± 0·08	6·45 ± 1·97
	Reserpine (3) (2–4 mg/kg i.p.)	42·35 ± 9·59	1·43* ± 0·45	0·49 ± 0·08	11·86 ± 2·19
Human	Control (5)	14·12 ± 4·65	0·30 ± 0·03	0·14 ± 0·06	0·11 ± 0·02

*$P < 0·05$ difference from mean of control.

Tyramine, cocaine and reserpine in the cat

The cats which had been used as controls in Table 1 were also used to investigate the responses to injection of tyramine, before and after cocaine. The injection of tyramine (0·1 to 0·4 mg/kg) invariably caused a decrease in pulmonary resistance (Table 2). This decrease in resistance did not appear to be dependent on dosage. The aortic blood pressure was invariably increased. Pulmonary compliance was decreased in four out of six cats, and was increased in the other two.

After the intravenous injection of cocaine (5 mg/kg), the blood pressure response to tyramine was reduced in four out of six cats. In the two remaining cats the pressor response before cocaine was reversed to a depressor response after cocaine. This effect of cocaine on the blood pressure response to tyramine is well known.

After the administration of cocaine, the injection of tyramine caused an increase in pulmonary resistance in four cats. In two cats, however, the initial bronchodilator action of tyramine was only reduced and not reversed by cocaine. There was a parallelism between the effect of cocaine on the blood pressure response and the bronchial response to tyramine. It is therefore suggested that the mechanism of the bronchodilator action of tyramine is similar to the mechanism of its pressor effect.

The effects of injecting tyramine in cats that have been pretreated with reserpine are also summarized in Table 2. The pressor response to tyramine was reduced by

TABLE 2. *Responses in cats to intravenous injections of tyramine, cocaine, noradrenaline and isoprenaline*

		Mean ± S.E.M.					
		Resistance		Compliance		Aortic BP	
Procedure	No. of animals*	Control†	% change	Control ml/cm H_2O	% change	Control mm Hg	% change
Tyramine 0·1 mg/kg	6 (A)	36·8±8·3	−20±3·3	4·8±0·7	0±0·0	81±11	+49±20
Tyramine 0·2 mg/kg	6 (A)	41·7±8·4	−21±5·8	4·6±0·9	−7±7·6	76±10	+76±22
Tyramine 0·3 mg/kg	2 (A)	24·5±3·5	−9±0·1	5·6±1·1	−7±0·8	92±17	+87±20
Tyramine 0·4 mg/kg	3 (A)	49·7±13·3	−30±9·0	2·5±0·2	+2±20·4	87±9	+54±9
Cocaine 5 mg/kg then tyramine 0·1 mg/kg	6 (A)	42·2±9·4	+24±7·1	4·1±0·8	−7±5·1	70±10	+2±5
Cocaine 5 mg/kg then tyramine 0·2 mg/kg	6 (A)	41·1±9·4	+39±8·1	4·2±0·9	+2±7·5	77±10	+29±22
Cocaine 5 mg/kg then tyramine 0·3 mg/kg	2 (A)	28·5±1·5	+15±4·0	3·9±1·3	−3±4·5	75±25	+18±7
Cocaine 5 mg/kg then tyramine 0·4 mg/kg	3 (A)	55·0±10·8	+5±6·3	2·5±0·3	+12±1·0	73±11	+16±5
Reserpine then tyramine 1 mg/kg	5 (B)	28·3±8·1	+7±16·1	4·8±0·8	−3±4·8	60±6	+65±4
After reserpine and noradrenaline (0·5 mg during 20 min) tyramine 1 mg/kg	5 (B)	30·2±5·6	+18±29·0	4·5±0·8	−13±10·3	70±9	+87±6
Reserpine then tyramine 1 mg/kg	4 (C)	31·1±9·4	+9±10·5	4·2±0·9	−10±7·9	58±10	+53±21
After reserpine and isoprenaline (0·5 mg during 20 min) tyramine 1 mg/kg	4 (C)	30·0±7·5	+8±12·4	5·0±1·2	+3±13·2	52±7	+28±4
Tyramine 0·2 mg/kg	5 (D)	32·3±1·3	−23±4·3	13·3±2·7	−15±1·9	121±7	+42±8
After tolazoline tyramine 0·2 mg/kg	5 (D)	33·4±1·3	−16±2·9	14·6±2·9	+16±4	74±2·4	−25±4
After sotalol tyramine 0·2 mg/kg	5 (D)	33·2±1·1	+2±2·2	14·4±2·9	0±4·5	70±3	−7±11

* There are four groups of cats summarized in this table. The results from individual groups are identified by A, B, C, and D.
† Resistance expressed in cm H_2O/litre per s.

reserpine treatment. The increase in blood pressure after an injection of tyramine (1 mg/kg) was 65% in one of the groups of cats treated with reserpine. To elicit an increase of 76% of the control blood pressure in the groups of cats without reserpine, a lower dose of tyramine (0·2 mg/kg) was required. The changes in pulmonary resistance initiated by tyramine in the cat after reserpine were variable. Two cats showed an increase in resistance, while three cats responded with a decrease.

The group of cats reported in the preceding paragraph received an infusion of noradrenaline (0·5 mg in 20 min) (Table 2). The injection of tyramine was repeated 15 min after infusion. In all five cats, the pressor effect of tyramine was potentiated. The bronchopulmonary effects of tyramine were not altered, however, and remained variable.

Another group of four cats that were pretreated with reserpine subsequently received an infusion of isoprenaline (0·5 mg in 20 min) (Table 2). There was no consistent pattern in the bronchopulmonary effects of tyramine after this treatment. One cat showed a conversion of the tyramine response from a reduction in resistance to an increase after the infusion of isoprenaline. Another cat showed the opposite effect following the infusion. The pressor effect of tyramine was not potentiated by isoprenaline.

Six of the cats that had been given reserpine had several samples of lung removed, following the injection of tyramine (1 mg/kg) and a noradrenaline infusion (totalling 0·5 mg in 20 min). The former did not influence the content of amines, whereas the latter caused a significant increase in the content of noradrenaline in the lung (Table 3).

Tolazoline and sotalol in the cat

In the last group of five cats, the types of sympathetic receptors responsible for the bronchopulmonary effects of tyramine were investigated. The initial injection of tyramine (0·2 mg/kg) caused a definite fall in pulmonary resistance (Table 2). Pulmonary compliance was reduced and the aortic blood pressure was elevated.

After tolazoline (4 mg/kg) was injected intravenously, the blood pressure dropped approximately 15 to 20% and remained at a level lower than in the control. The bronchopulmonary effects of tolazoline were variable. After 5 min, the pulmonary resistance, pulmonary compliance and blood pressure became stable and the injection of tyramine (0·2 mg/kg) was repeated. This second injection of tyramine in the same dose as before still reduced the pulmonary resistance, although the decrease was smaller than before tolazoline. The compliance was increased, while before tolazoline it was decreased. The pressor response to tyramine was also reversed to depressor by tolazoline.

TABLE 3. *Content of biogenic amines in the lung of cats receiving reserpine, tyramine and noradrenaline*

Procedure	No. of animals	Mean±S.E.M. (μg/g lung) Histamine	5-HT	Noradrenaline	Dopamine
Reserpine 3 mg/kg	6	13·20±2·88	1·61±0·27	0·07±0·03	0·10±0·10
Then tyramine 1 mg/kg	6	12·01±4·33	1·28±0·21	0·10*±0·04	0·09±0·05
Then noradrenaline infusion (0·5 mg during 20 min)	6	10·31±2·02	1·31±0·19	0·48†±0·12	0·10±0·04

* $P<0·02$ difference from mean value after receiving reserpine only.
† $P<0·02$ difference from mean value after receiving tyramine before noradrenaline.

Fifteen min after the injection of tolazoline, sotalol (2 mg/kg) was injected. Five min later, another dose of tyramine was injected. The reduction of pulmonary resistance disappeared. The bronchodilator effect of tyramine therefore seems to be blocked by sotalol. The changes in compliance and blood pressure in response to tyramine remained variable after the injection of sotalol.

Tyramine in the rabbit

The responses to tyramine were different from those elicited by dopamine in the same group of rabbits (Table 4). An intravenous injection of tyramine (2 mg/kg) produced a decrease in pulmonary resistance, an increase in pulmonary compliance and a rise in aortic blood pressure. In one rabbit, after tolazoline, tyramine still produced a fall in resistance, but the pressor effect was reversed to a depressor (not shown in Table 2).

Dopamine in the rabbit

The next group, consisting of five rabbits, was used to study the response to intravenous injection of dopamine (10 mg/kg) before and after tolazoline ; the results are summarized in Table 4. Initially, dopamine caused a rise in pulmonary resistance, a fall in compliance and a fall in aortic blood pressure. After tolazoline all three responses to dopamine were reversed, showing a reduction in resistance, increase in compliance and a rise in blood pressure.

Dopamine in the cat

The intravenous injection of dopamine (10 μg/kg) into the cat caused a small increase in pulmonary resistance in four out of five cats tested.

Dopamine in the dog

Table 5 summarizes the responses to dopamine injection in two control groups and a group that had received reserpine. In the control dogs there was an increase in pulmonary resistance and systemic blood pressure, accompanied by variable changes in compliance. In some dogs there was a biphasic rise and fall in aortic blood pressure. The dogs that were pretreated with reserpine did not reveal any change in the response to dopamine.

Some of the dogs that did not receive reserpine were given repeated injections of dopamine before and after sympathetic receptor blocking drugs (Table 5). The pressor response was blocked or reversed by intravenous injection of tolazoline (4 mg/kg). The depressor component was not blocked by sotalol. The pulmonary

TABLE 4. *Responses in rabbits to intravenous injections of tyramine and dopamine*

		Mean ± S.E.M.					
		Resistance		Compliance		Aortic BP	
Procedure	No. of animals	Control*	% change	Control ml/cm H_2O	%change	Control mm Hg	% change
Tyramine 2 mg/kg	5	38·8±1·8	−6±6·9	4·3±0·4	+18±4·3	70±5	+27±7
Dopamine 10 μg/kg	5	36·5±3·2	+14±3·7	4·8±0·3	−14±5·7	91±11	−22±3
After tolazoline dopamine 10 μg/kg	3	47·9±2·9	−6±2·4	4·3±0·3	+19±8	53±6	+71±8

* Resistance expressed in cm H_2O/litre per s.

resistance was increased slightly and compliance was decreased following most injections of dopamine before the blocking drugs. When dopamine was injected after tolazoline, its effect on pulmonary resistance was either blocked or reversed and the decrease in compliance was also blocked. After the injection of sotalol (2 mg/kg), an increase in pulmonary resistance in response to dopamine was observed in all the dogs.

Dopamine in the goat

The intravenous injection of dopamine invariably caused an increase of pulmonary resistance (Table 6). At a dose of 1 μg/kg, the lowest dose of dopamine tested in a goat, there was a slight increase in pulmonary resistance, lasting for 3 min. There was also a concomitant rise in compliance without any change in the aortic blood pressure and the pulmonary arterial blood pressure. These changes occurred in one goat but did not appear in a second goat.

With larger doses (10 and 100 μg/kg) the increase in pulmonary resistance was evident within 10 s after injection and was maintained at that level with slight fluctuations during the whole period of measurement (5 to 6 min). Pulmonary compliance was either increased or decreased. At 15 to 20 min after the injection, however, when the control value for the next injection was measured, the compliance and resistance had returned to values comparable with the original control level or lower but never to a higher level.

TABLE 5. *Responses in dogs to intravenous injections of dopamine*

		Mean ± S.E.M.					
		Resistance		Compliance		Aortic BP	
Procedure	No. of animals*	Control†	% change	Control ml/cm H_2O	% change	Control mm Hg	% change
Dopamine 10 μg/kg	5 (A)	7·4±0·5	+9±4·8	22·0±0·8	−3±5·4	120±7	+37±6
After tolazoline (4 mg/kg) dopamine 10 μg/kg	5 (A)	7·7±0·8	−5±3·1	24·2±1·2	−2±1·6	117±6	−12±5
After sotalol (2 mg/kg) dopamine 10 μg/kg	5 (A)	7·8±0·7	−6±1·2	23·4±0·7	−3±2·3	101±9	−8±5
After reserpine (3 mg/kg) dopamine 10 μg/kg	3 (B)	9·7±1·8	+8±5·2	24·3±1·3	−7±3·5	83±9	+33±7
No reserpine dopamine 10 μg/kg	8 (C)	7·1±0·8	+6±2·7	29·4±2·5	+2±1·8	122±7	+3±8

* There are three groups of dogs summarized in this table. The results from individual groups are identified by A, B, and C.
† Resistance is expressed as cm H_2O per litre per s.

TABLE 6. *Responses in goats to intravenous injections of dopamine*

		Mean ± S.E.M.					
		Resistance		Compliance		Aortic BP	
Procedure	No. of animals*	Control†	% change	Control ml/cm H_2O	% change	Control mm Hg	% change
Dopamine 10 μg/kg	3 (A)	14·3±2·4	+13±4·8	16·9±1·6	+1±8·3	67±22	+15±7
Dopamine 100 μg/kg	5 (A)	11·8±0·9	+17±2·8	18·8±1·7	+4±4·2	90±8	+36±11
After reserpine dopamine 100 μg/kg	2 (B)	13·5±3·0	+9±8·6	34·5±3·5	−8±9·7	56±1	+40±24

* There are two groups of goats summarized in this table. The results from individual groups are identified by A and B.
† Resistance expressed as cm H_2O per litre per s.

In the two goats pretreated with reserpine, the injection of dopamine (100 μg/kg) elicited an increase in pulmonary resistance similar to that seen in the goats not treated with reserpine (Table 6). The change in pulmonary compliance did not show any consistent pattern and fluctuated in an unpredictable way. The pulmonary arterial pressure was invariably increased by dopamine ; the aortic pressure was usually increased, except in one goat in which a decrease was seen. There was no significant difference in the responses to dopamine between the controls and the animals receiving reserpine.

Discussion

The content of noradrenaline in the lungs of various species investigated are summarized in Table 7. Our results in general agree with the values obtained by Carlsson (1959). Reserpine causes a fall in the noradrenaline content of the lung in all the animals tested except in the rabbit and goat. This indicates that noradrenaline is more resistant to reserpine in these animals than in the other species. It was also shown that the lung of the reserpine-treated cat can take up and store noradrenaline.

At least part of the noradrenaline present in the lung is contained in the sympathetic nerves innervating the various structures of the lung. The evidence that the bronchodilator fibres are adrenergic is mainly pharmacological. Lockett (1957) observed that the sympathetic bronchodilator fibres can be blocked by compound TM-10 (Choline 2 : 6-xylyl ether bromide), which is thought to act by preventing the release of the transmitter substance. Daly & Mount (1951) noted that response to stimulation of the bronchodilator fibres can be potentiated by cocaine, an effect thought to be mediated by an action on the adrenergic fibres. Furthermore, Lockett (1957) has reported the release of an isoprenaline-like substance in the perfusate of the cat heart-lung preparation, following electrical stimulation of the thoracic sympathetic chain. Muscholl & Vogt (1958), however, used more stringent methods of identification and were unable to confirm the release of isoprenaline.

Our experiments on the cat have contributed some relevant information. The bronchodilator action of tyramine was reduced by cocaine and by reserpine. But

TABLE 7. *Noradrenaline content in mammalian lung*

Animal	Noradrenaline (μg/g)	Method of assay	Author
Mouse	0·11±0·01	Fluorometric	Aviado & Sadavongvivad (1970)
Rat	0·1	Fluorometric	Carlsson (1959)
	0·18±0·02	Fluorometric	Sadavongvivad (1970)
Guinea-pig	0·2	Fluorometric	Carlsson (1959)
	0·16±0·02	Fluorometric	Sadavongvivad (1970)
Rabbit	0·0	Fluorometric	Carlsson (1959)
	0·18±0·02	Fluorometric	Sadavongvivad (1970)
Cat	0·3	Fluorometric	Carlsson (1959)
	0·47±0·08	Fluorometric	This article
Dog	0·1	Fluorometric	Carlsson (1959)
	0·35±0·02	Fluorometric	This article
Goat	0·1	Fluorometric	Carlsson (1959)
	0·39±0·08	Fluorometric	This article
Human	0·14±0·06	Fluorometric	This article

the bronchodilatation was not restored after infusion of either noradrenaline or isoprenaline. The suppressive effect of cocaine on the bronchodilatation induced by tyramine suggests that the bronchodilator nerves are adrenergic. The failure of an infusion of either noradrenaline or isoprenaline to restore the bronchodilator action of tyramine suggests further that neither of these two substances is the probable transmitter. This interpretation is based on the assumption that tyramine acts on the bronchial passages by releasing from the bronchodilator nerves an adrenergic transmitter in a manner similar to the action of tyramine on the cardiovascular system.

The effects of tyramine on the aortic blood pressure of the rabbit, cat and dog, reported above, conform with those reported in the literature (Muscholl, 1966). It is generally believed that tyramine produces its pressor effect by releasing noradrenaline from the adrenergic nerves innervating the blood vessel wall.

The bronchopulmonary effects of tyramine are more complex than the cardiovascular effects. The results obtained from experiments involving blocking agents support the theory of the adrenergic nature of the mechanism responsible for the bronchodilatation induced by tyramine. In the rabbit and cat, the bronchodilatation is not blocked by tolazoline, an α-adrenoceptor blocking drug, but is completely blocked or reversed by sotalol, a β-adrenoceptor blocking drug.

The mean values for the content of dopamine in the lungs of all the mammalian species studied in this investigation are summarized in Table 8. The high value for dopamine in the goat reported by Carlsson (1959) is confirmed in the present investigation. The values reported for all other species are generally higher than those reported by Carlsson. These values are open to criticism because our method may not be sensitive enough for this low concentration of dopamine. However, the general pattern of low dopamine concentrations in all mammalian species except the ruminants, as found by other investigators, is confirmed by our results.

The concentration of dopamine in the lung is not affected by the various procedures reported above. It can be seen that dopamine in the lung is highly resistant to the administration of various drugs and to pathological processes. In the goat, where the dopamine has been shown to be stored in the mast cells, reserpine failed to cause any depletion.

One of the conclusions reached in this study is that dopamine can cause an increase in pulmonary resistance. This was demonstrated in the rabbit, cat, dog and

TABLE 8. *Dopamine content in mammalian lungs*

	Dopamine (μg/g)	Method of assay	Author
Mouse	0·15±0·04	Fluorometric	Aviado & Sadavongvivad (1970)
Rat	0·0	Fluorometric	Carlsson (1959)
	0·19±0·02	Fluorometric	Sadavongvivad (1970)
Guinea-pig	0·22±0·03	Fluorometric	Sadavongvivad (1970)
Rabbit	0·2	Fluorometric	Carlsson (1959)
	0·30±0·05	Fluorometric	Sadavongvivad (1970)
Cat	0·0	Fluorometric	Carlsson (1959)
	0·44±0·09	Fluorometric	This article
Dog	0·0	Fluorometric	Carlsson (1959)
	0·24±0·05	Fluorometric	This article
Goat	5·3	Fluorometric	Carlsson (1959)
	6·45±1·97	Fluorometric	This article
Human	0·59±0·36	Fluorometric	This article

goat. The rabbit and goat seem to be relatively more sensitive than the cat and the dog. This effect of dopamine has not previously been reported. It is generally believed that dopamine has no bronchomotor action (Daly & Hebb, 1966). The only study on the bronchomotor action of dopamine was reported by Waaler (1961), who failed to elicit any bronchomotor response in the isolated lung lobe of the dog. The method used by Waaler (1961) for measuring the bronchomotor response was the ventilation overflow method of Konzett & Rossler (1940). This method has low sensitivity and measures pulmonary compliance rather than resistance. The change in tidal air measured by the Konzett & Rossler method may also be due to change of blood volume in the lung (Barer & Nusser, 1953).

In this study the increase in pulmonary resistance caused by dopamine was demonstrated to be due to a direct stimulation of the α-adrenoceptors in the bronchial smooth muscle. In the rabbit, the effect of dopamine is reversed by α-adrenoceptor blocking agents. In the dog, the increase in pulmonary resistance can be blocked by an α-adrenoceptor blocking agent but not by a β-adrenoceptor blocking agent. In the cat, however, the increase in pulmonary resistance is not effectively blocked by either type of blocking agent.

The action of dopamine on the pulmonary resistance, although definite, is very slight even at high doses. This, coupled with the generally low dopamine content in the lung of most animals, would tend to obviate the suspicion of any physiological importance of dopamine in altering the bronchomotor tone. In the species in which the content of dopamine in the lung is low, dopamine probably serves only as a precursor for the synthesis of sympathetic transmitters. In the ruminant lung the concentration of dopamine is very high and appears to be located in the mast cells (Bertler, Falck, Hillarp, Rosengren & Torp, 1959 ; Coupland & Heath, 1961 ; Falck, Nystedt, Rosengren & Stenflo, 1964).

In this study it is shown that dopamine can cause an increase in pulmonary resistance in the goat. The same effects have been seen with 5-hydroxytryptamine and histamine (unpublished). Further investigation is required to test whether any one of these amines is released into the bronchial blood draining the airways. The situation for the release of dopamine may prove to be similar to that for the release of histamine, in which blood analysis is more helpful than lung analysis. Now that lung analysis has been completed, the interest can turn to the chemical analysis for any dopamine released in the blood.

This work was supported by a grant from the Council for Tobacco Research, New York City. This publication is based in part upon the thesis submitted by C. Sadavongvivad in fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmacology, University of Pennsylvania.

REFERENCES

AVIADO, D. M. & SADAVONGVIVAD, C. (1970). Pharmacological significance of biogenic amines in the lungs: histamine. *Br. J. Pharmac.*, **38**, 366–373.

BARER, G. R. & NUSSER, E. (1953). The part played by bronchial muscle in pulmonary reflexes. *Br. J. Pharmac. Chemother.*, **8**, 315–320.

BERTLER, A., FALCK, B., HILLARP, N. A., ROSENGREN, E. & TORP, A. (1959). Dopamine and chromaffin cells. *Acta physiol. scand.*, **47**, 251–258.

BERTLER, A. & ROSENGREN, E. (1959). Occurrence and distribution of dopamine in brain and other tissues. *Experientia*, **15**, 10.

CARLSSON, A. (1959). The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmac. Rev.*, **11**, 490–493.

CASTRO DE LA MATA, R., PENNA, M. & AVIADO, D. M. (1962). Reversal of sympathomimetic bronchodilatation by dichloroisoproterenol. *J. Pharmac. exp. Ther.*, **135**, 197–203.

COUPLAND, R. E. & HEATH, I. D. (1961). The chromaffin cells of the liver capsule and gut in ungulates. *J. Endocr.*, **22**, 71–76.

DALY, I. de B. & HEBB, C. (1966). *Pulmonary and Bronchial Vascular Systems*, pp. 202–248. Baltimore: Williams & Wilkins Co.

DALY, M. DE B. & MOUNT, L. E. (1951). The origin, course, and nature of bronchomotor fibres in the cervival sympathetic nerve of the cat. *J. Physiol., Lond.*, **113**, 43–62.

EULER, U. S. VON & LISHAJKO, F. (1957). Dopamine in mammalian lung and spleen. *Acta physiol. pharmac. neerl.*, **6**, 295–303.

FALCK, B., NYSTEDT, T., ROSENGREN, E. & STENFLO, J. (1964). Dopamine and mast cells in ruminants. *Acta pharmac. tox.*, **21**, 51–58.

FOLLE, L. E. & AVIADO, D. M. (1965). Cardiovascular effects of anoxia and the influence of a new beta adrenergic receptor blocking drug. *J. Pharmac. exp. Ther.*, **149**, 79–90.

KLIDE, A. M. & AVIADO, D. M. (1967). Mechanism for the reduction in pulmonary resistance induced by halothane. *J. Pharmac. exp. Ther.*, **158**, 28–35.

KONZETT, H. & ROSSLER, R. (1940). Versuchsanordnung zu Untersuchungen an der Bronchialmuskulatur. *Arch. exp. Path. Pharmak.*, **195**, 71–74.

LOCKETT, M. F. (1957). The transmitter released by stimulation of the bronchial sympathetic nerves of cats. *Br. J. Pharmac. Chemother.*, **12**, 86–96.

MUSCHOLL, E. (1966). Indirectly acting sympathomimetic amines. *Pharmac. Rev.*, **18**, 551–559.

MUSCHOLL, E. & VOGT, M. (1958). The action of reserpine on the peripheral sympathetic system. *J. Physiol., Lond.*, **141**, 132–155.

PAASONEN, M. K. & KRAYER, O. (1958). The release of norepinephrine from the mammalian heart by reserpine. *J. Pharmac. exp. Ther.*, **123**, 153–160.

SADAVONGVIVAD, C. (1970). Pharmacological significance of biogenic amines in the lungs: 5-hydroxytryptamine. *Br. J. Pharmac.*, **38**, 353–365.

WAALER, B. A. (1961). Effect of dopamine on the isolated perfused lung lobes of the dog. *Br. J. Pharmac. Chemother.*, **16**, 195–202.

(*Received July* 4, 1969)