Pulmonary Vascular Responses to Serotonin and Effects of Certain Serotonin Antagonists

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Serotonin was the most potent pulmonary vasoconstrictor studied in an experimental preparation in which drugs injected into the pulmonary artery are temporarily excluded from the systemic circulation. Alterations in bronchomotor tone did not approach those produced by acetylcholine. Simultaneous systemic vascular or cardiac reflexes were not noted. Promethazine, LSD-25 and its 2-brom derivative were potent blockers of serotonin effects in the pulmonary circulation.

CARDIOVASCULAR responses to serotonin have been extensively studied by many groups of investigators, most of whom have noted that this agent increases pulmonary vascular resistance. Some have detected systemic vascular reflexes initiated by serotonin in the pulmonary circulation. Several investigations have indicated that certain substances, some of them structurally related to serotonin, may modify its vascular effects. In the present investigation, serotonin was studied with an experimental system in which drugs injected into the pulmonary circulation of intact dogs can be prevented for a time from entering the systemic circulation. The direct effects of serotonin on the pulmonary circulation were observed, with particular attention to simultaneous indirect effects on the systemic circulation and heart. A series of representative compounds was studied for antagonism to serotonin in the pulmonary vessels. Thus a technic designed primarily for the study of pulmonary vasomotor activity permitted the investigation of several pharmacologic properties of serotonin.

METHODS

Observations were made in 24 anesthetized, open-chest, mongrel dogs weighing between 10 and 17 Kg. Sixteen were anesthetized with intravenous sodium pentobarbital (25 mg./Kg.). In 8 dogs, urethane 1.5 to 3.5 Gm./Kg. intraperitoneally was used instead. In 20 dogs respirations were maintained with 100 per cent oxygen delivered by a variable phase pulmotor valve to an endotracheal tube. Four dogs were maintained on a Starling "Ideal" respirator.

A hydraulically operated, controlled-output pump was substituted for the left ventricle in each animal, by means of technics and apparatus previously described in detail.2 Blood was drained totally from the left atrium into a reservoir via a 3/8 inch Tygon tube. From the reservoir, it was pumped to a T-tube in the descending thoracic aorta. Left ventricular bypass was complete. The right ventricle continued to function effectively, keeping pace with the mechanical pump. Stroke volume and rate of the mechanical pump were kept constant at levels between 1.5 and 2.4 L./min. In this preparation pump output does not vary with alterations in peripheral resistance.

The modification by which effects of drugs in the pulmonary circulation were studied has also been described in detail. As serotonin was injected into the main pulmonary artery (or right heart via an intracardiac catheter), the tube draining the left atrium was diverted temporarily to a second reservoir. The systemic circulation continued to be maintained with blood pumped into the aorta from the main pump reservoir. When the main reservoir was near depletion, the left atrial tube was returned to its original position. Then, after an interval, the blood and drug in the temporary container were returned to the experimental system and effects in the systemic circulation were recorded.

FIG. 1. Original record of injection of 20 serotonin into pulmonary artery in the pump preparation. (Urethane anesthesia, Starling respirator, hematocrit - 50.) At A, the left atrial tube was diverted to the temporary reservoir; at B, injection was made; at C, left atrial tube was returned to its original position. Between B and C, serotonin traversed only the lungs. At D, blood in the temporary reservoir (containing the serotonin that had traversed the lungs) was returned to the experimental system. (Paper speeds: 1.0 and 25 mm./sec.)

In the two-hour period, no hemodynamic alterations occurred.

Pulmonary vasomotor responses to serotonin were not altered by bilateral cervical vagotomy. Increases of 66 and 122 per cent were observed. During the period in which serotonin was used, the left atrial pressure remained normal (1 to 7 mm. Hg). The systemic arterial pressure showed no changes.

Aortic pressure, pulmonary arterial pressure, and endotracheal or "airway" pressure were directly recorded by means of strain-gage transducers. Pulmonary venous flow was directly recorded with a Shipley-Wilson rotameter on the left atrial drainage tube. Left atrial pressure remained constant at normal levels (1 to 7 mm. Hg) during each measurement period.

Pulmonary injection volumes never exceeded 1 ml. The 5-hydroxytryptamine used in this study was serotonin creatinine sulfate complex. All doses given refer to serotonin base. All pulmonary arterial injections were made at 5 min. intervals.

Substances studied for modification of the pulmonary vascular effects of serotonin were administered intravenously after several control observations. Serotonin injections were repeated after the circulation was restabilized. Drugs studied for serotonin blocking activity included: lysergic acid diethylamide (LSD-25); its 2-brom derivative, 2-bromlysergic acid diethylamide (brom-LSD); L-benzyl-2, 5-dimethylserotonin (BAS); promethazine (Phenergan); tripelennamine (Pyribenzamine); chlorprophenpyridamine (Chlor-Tri-meton); tolazoline (Priscoline), and reserpine. The doses of these substances are given below.

RESULTS

Pulmonary Vasomotor Responses. In 24 dogs, 116 observations were made. Sixty-four of these were not preceded by another drug under study for antiserotonin properties. Effective doses used ranged from 1.5 to 80 mcg./Kg. (Fig. 1). Between the times designated B and C (see legend for experimental details) the serotonin injected into the pulmonary artery was confined to the pulmonary circulation. An immediate increase in pulmonary vascular resistance was evidenced by the prompt rise in pulmonary arterial pressure and fall in pulmonary venous flow. The immediate increase in pulmonary vascular resistance was unmodified by the subsequent administration of other substances. Figure 1 shows a typical response. In the dose range 1.5 to 8.5 mcg./Kg., 47 injections were made resulting in pulmonary vascular resistance increases of 6 to 200 per cent (mean 53 per cent, S.D. ± 42). In the close range 20 to 47 mcg./Kg., 15 injections were made resulting in an increase of 22 to 130 per cent (mean 62 per cent, S.D. ± 36). Two injections of 80 mcg./Kg. caused increases of 66 and 122 per cent.

Pulmonary vascular responses to serotonin were not altered by bilateral cervical vagotomy in 2 dogs.

Simultaneous Systemic Effects. Figure 1 demonstrates that while serotonin is confined to the lungs, no simultaneous alterations occurred that could be attributed to the systemic administration of serotonin. The lungs and main extrapulmonary vessels were excluded from the systemic circulation.
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Curiously, systemic arterial pressure or heart rate (measured by counting pressure pulses in the pulmonary artery tracing). In no instance were systemic vascular or cardiac responses noted while serotonin was confined to the pulmonary vasculature.

Bronchomotor Effects. Responses in endotracheal or airway pressure to serotonin injections in the pulmonary artery were mild and variable. Endotracheal pressure increases never exceeded 25 percent of the control value. Of the 64 observations, no airway pressure change was observed in 28. Airway pressure rose immediately following the pulmonary artery injection (as in fig. 1) in 15 instances, and it rose only after serotonin entered the systemic circulation in 21. Airway pressure changes were not altered by bilateral cervical vagotomy in two dogs that exhibited elevations immediately after pulmonary arterial injections.

Serotonin Antagonists. When serotonin was administered in identical doses at 5 minute intervals, no tachyphylaxis was observed. This phenomenon permitted study of blockers of serotonin pulmonary vascular effects in sequence. An example of this method of study is shown in figure 2. Promethazine, LSI and brom-LSD were approximately equally active in antiserotonin effect in the pulmonary vasculature. The smallest doses of these substances which completely blocked the rise in pulmonary vascular resistance were promethazine, 0.6 mg./Kg.; LSI-25, 0.4 mg./Kg. and brom-LSD, 0.6 mg./Kg. The smallest completely effective dose of HAS was 1.8 mg./Kg. Duration of effect of antiserotonin substances was not studied systematically. Chlorprophenpyridamine, tripelennamine, tolazoline and reserpine were all without antiserotonin properties in doses as high as 2.0 mg./Kg. A final observation is that substances capable of blocking the pulmonary vascular effects of serotonin, when injected intravenously, themselves produced variable, but sometimes striking, elevations of pulmonary vascular resistance.

Discussion

Our study of serotonin stemmed from an interest, not in its pharmacologic properties, but in its pulmonary vasoconstrictor activity. In the recent past, pulmonary vascular resistance changes produced by drugs were attributed to changes produced by drugs were attributed to redistribution of blood volume,13 elevated left atrial pressure,11 or altered bronchomotor tone.12 In our laboratory and others,11-17 experiments that excluded extrapulmonary factors demonstrated that these effects were due in whole or in part to pulmonary vasoconstrictor activity. Notable in this regard are the recent studies of Borst, Berglund and McGregor,18 which demonstrated the by guest on April 13, 2017 http://circres.ahajournals.org/ Downloaded from
potent, direct pulmonary vascular effects of serotonin. Serotonin is the most potent constrictor of the pulmonary vasculature that has been studied in our preparation. Although not studied in the same dogs, constricting doses of serotonin were much lower than those of acetylcholine and epinephrine and norepinephrine used in previous studies. Histamine is overshadowed by serotonin (unpublished). In addition, there are qualitative differences between the direct pulmonary effects of serotonin and acetylcholine. When acetylcholine raises pulmonary vascular resistance, the effect is accompanied by a consistently large increase in airway pressure. Borst and his co-workers demonstrated that the increased pulmonary vascular resistance produced by acetylcholine and histamine is diminished when the bronchial tree is airless.

There is still no evidence for the mechanism or pathway whereby a drug injected into the pulmonary artery produces alterations in bronchomotor tone. In the present experiments and in those on effects of acetylcholine, responses were not altered by vagotomy, suggesting that both vascular and bronchial effects are elicited directly by the drug rather than by reflex stimulation. This merely confirms the detailed studies of Konzett, who investigated serotonin-induced bronchoconstriction in cats and guinea pigs.

Serotonin appears to affect the bronchi via the pulmonary artery, via the systemic (bronchial) circulation, or by both pathways. It is possible that drugs enter the bronchial capillary or venous circulation by way of pulmonary-bronchial anastomoses, or that terminal respiratory units provided with sufficient smooth muscle to produce elevations of airway pressure are supplied by the pulmonary artery.

On the basis of experiments in cats, Conroe and his colleagues suggested that serotonin elicits a reflex in the pulmonary vasculature that results in altered systemic arterial pressure. This was considered a possible mechanism, but the results in intact animals were not reproduced by the present study. Further experiments with serotonin antagonists in intact animals are needed to resolve this question. The present study shows that serotonin is not effective in altering systemic arterial pressure in intact animals, and it is clear that this drug does not elicit a systemic vasodilator response in intact animals.

SUMMARY

The effects of serotonin on the pulmonary vascular bed of intact dogs were studied in an experiment in which the drug could be excluded temporarily from the systemic circulation. This agent was the most potent constrictor of the pulmonary blood vessels studied. Serotonin differed qualitatively from other pulmonary vasoconstrictors, failing to elicit simultaneously the degree of bronchoconstriction seen with acetylcholine and histamine. Systemic vascular reflexes were not initiated by serotonin in the pulmonary vessels, in an experimental preparation in which such reflexes are easily demonstrated. The reproducibility of effect when this substance was administered at at least 5 min. intervals permitted investigation of pharmacologic antagonism to serotonin in the pulmonary vasculature.
The pharmacologic effect of serotonin in the lungs. Promethazine, lysergic acid diethylamide and its 2-brom derivative were the most potent agents studied in this regard.

Acknowledgments
The authors are grateful to Miss Lois Reed and Mr. Thomas F. Doyle, who provided valuable technical assistance. Dr. Arthur Pallotta, Hazleton Laboratories, Falls Church, Virginia, generously supplied LSD-25, broin-LSD and BAS.

Addendum
Since acceptance of this manuscript, W. H. Knisely has personally communicated the observation that, following intravenous injection of serotonin in animals, whitish translucent material visibly embolized small pulmonary arteries (Fed. Proc. 17: 88, 1958). Knisely and his colleagues suggest that increased pulmonary vascular resistance due to serotonin may be due, in whole or in part, to transient embolization.

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Circ Res. 1958;6:283-288
doi: 10.1161/01.RES.6.3.283

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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