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 given to the simultaneous indirect effects on the systemic circulation. 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 vasomotion has 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 six 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. 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 by-pass 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 measured. A transient hypotension following the return of the left atrial tube was noted in most experiments. The systemic circulation was affected minimally by the hypotension and the hypotension was not substituted for the left ventricle in the experiment. When hypotension occurred, the hypotension was corrected by the administration of ephedrine or by the slow intravenous administration of normal saline solution. The atrial tube was returned to its original position before the hypotension reached a critical value.

In the present investigation, serotonin was administered by intravenous injection and by direct injection into the pulmonary artery via a catheter. Serotonin was administered in a dose of 0.1 mg./kg. to 1 mg./kg. intravenously, or in a dose of 0.01 mg./kg. to 0.1 mg./kg. into the pulmonary artery. The time required for the maximum response to serotonin was studied in each animal. The maximum response to serotonin was measured in each animal and was expressed as a percentage of the control value.

The effects of a variety of compounds on the pulmonary vascular response to serotonin were studied. The compounds were administered intravenously or by direct injection into the pulmonary artery. The compounds included drugs that have been reported to have a direct effect on the pulmonary circulation, drugs that have been reported to have a direct effect on the systemic circulation, and drugs that have been reported to have a direct effect on both the pulmonary and systemic circulations. The effects of these compounds on the pulmonary vascular response to serotonin were measured and compared with the effects of serotonin alone.

The results of the present investigation indicate that serotonin is a potent pulmonary vasoconstrictor. The pulmonary vascular response to serotonin was potentiated by the administration of norepinephrine or by the injection of serotonin into the pulmonary artery. The pulmonary vascular response to serotonin was inhibited by the administration of a variety of compounds, including drugs that have been reported to have a direct effect on the pulmonary circulation, drugs that have been reported to have a direct effect on the systemic circulation, and drugs that have been reported to have a direct effect on both the pulmonary and systemic circulations.

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FIG. 1. Original record of injection of 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 G, 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.)

Circulation were observed. During the period in which the left atrial tube was diverted from the main pump reservoir, serotonin traversed only the lungs and was excluded from the systemic circulation.

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 the 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-Triamteren); 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 

ng./Kg. Figure 1 shows a typical response. Between the times designated B and C (see figure 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. (In this instance, pulmonary vascular resistance rose 100 per cent.) After C, serotonin was present in the systemic circulation and produced variable effects, sometimes increasing and sometimes decreasing systemic vascular resistance. In several instances, the dose of serotonin capable of producing obvious increases in pulmonary vascular resistance was insufficient to produce detectable alterations in the systemic circulation.

No dose-response relationships could be established for the group, as illustrated by the following data. In the dose range 1.5 to 8.5 ng./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 ng./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 ng./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 in the systemic arteries. The lungs were isolated from the systemic circuit by a Y-connector and pump for the pulmonary circuit. The pump was reconnected to the systemic circuit at the Y-connector after each injection of serotonin. When serotonin was injected into the pulmonary artery, an immediate increase in pulmonary vascular resistance was evidenced by the prompt rise in pulmonary arterial pressure and fall in pulmonary venous flow. (In this instance, pulmonary vascular resistance rose 100 per cent.) Figure 1 shows a typical response. Between the times designated B and C (see figure 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. (In this instance, pulmonary vascular resistance rose 100 per cent.) After C, serotonin was present in the systemic circulation and produced variable effects, sometimes increasing and sometimes decreasing systemic vascular resistance. In several instances, the dose of serotonin capable of producing obvious increases in pulmonary vascular resistance was insufficient to produce detectable alterations in the systemic circulation.

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cur iu 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 per cent 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 min. 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, L51) 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.; LSD-25, 0.4 mg./Kg. and brom-LSD, 0.6 mg./Kg. The smallest completely effective dose of SRS 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 vasomotor 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 flow, elevated left atrial pressure, or altered bronchomotor tone. In our laboratory and others, experiments that excluded extrapulmonary factors demonstrated that these effects were due in whole or in part to pulmonary vasomotor activity. Notable in this regard are the recent studies of Borst, Berglund and McGregor, which demonstrated that the pulmonary arterial pressure and flow decrements seen in response to the inhalation of serotonin were not due to redistribution of blood flow, and that the pulmonary arterial pressure and flow decrements seen in response to the inhalation of serotonin were due to pulmonary vasomotor effects, not to redistribution of blood flow.

In our study of serotonin stimulations, we noted that serotonin injections into the pulmonary artery produced an immediate and sustained rise in pulmonary arterial pressure and flow. These effects were not altered by bilateral cervical vagotomy. The most striking feature of the response was the absence of any depression of systemic arterial pressure. The pulmonary vascular response, therefore, was a direct effect of serotonin on the pulmonary vasculature, not on the systemic circulation.

The pulmonary vascular response to serotonin was compared with the response to endogenous serotonin, which was elicited by administration of serotonin antagonist, or by the administration of serotonin antagonist itself. The pulmonary vascular response to serotonin antagonist was similar in magnitude to the response to serotonin. The pulmonary vascular response to serotonin antagonist was similar in magnitude to the response to serotonin.

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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 vasculature, in an experimental preparation in which such reflexes are easily demonstrated. The reproducibility of effect when this substance was administered at least 5 min. intervals permitted investigation of pharmacologic antagonism to serotonin in the pulmonary vascular bed.

**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 vasculature, in an experimental preparation in which such reflexes are easily demonstrated. The reproducibility of effect when this substance was administered at least 5 min. intervals permitted investigation of pharmacologic antagonism to serotonin in the pulmonary vascular bed.
The antagonists of serotonin and lungs. Promethazine, lysergic acid diethylamide and its 2-brom derivative were the most potent agents studied in this regard.

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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.

SUMMARY IN INTELLIGENT LANGUAGE
The effects that serotonin exerts over the vascular system of intact dogs were studied in an experiment in which the drug could be excluded temporarily from the systemic circulation. Among the agents studied, serotonin was the most potent constrictor of pulmonary blood vessels. It differed from other pulmonary vasoconstrictors in that it did not evoke simultaneously the degree of bronchoconstriction that results from the use of acetylcholine and histamine. Systemic vascular reflexes were not apparent post use of serotonin in an experimental preparation in which they would be easily demonstrable. The reproducibility of the effect when the substance was administered at intervals of at least 5 minutes permitted the investigation of pharmacological antagonism to serotonin in the lungs. In this respect, promethazine, diethylamido of lysergic acid, and its 2-brom derivative were the most potent agents studied.

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