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 has permitted the investigation of several pharmacologic properties of serotonin.

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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. 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 studied. The pulmonary circulation was subjected to the effects of drugs in an experimental system in which studies with an experimental system in which normal or diseased pulmonary vessels were studied were substituted for the effects on thenormal vessel. A pulmonary arterial pressure curve was obtained before and after each experiment to determine the individual effects on pulmonary blood flow and vascular resistance.
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FIG. 1. Original record of injection of 20 &mu;g 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 and was excluded from the systemic circulation. (Paper speeds: 1.0 and 25 mm./sec.)

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 vasomotor effects of serotonin included: lysergic acid diethylamide (LSD-25); its 2-brom derivative, 2-bromlysergic acid diethylamide (brom-LSD); 1-benzyl-2,5-dimethylserotonin (BAS); promethazine (Phenergan); tripelennamine (Pyribenzamine); chlorprophenpyridamine (Chlor-Tri); diethylpropion (Tropitone); and reserpine. The doses of these substances are given below.

RESULTS

Pulmonary Vascular 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 &mu;g./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 serotonin was present in the systemic circulation, no simultaneous alterations occurred in the systemic circulation. Pulmonary injection volumes never exceeded 1 ml. An immediate increase in pulmonary vascular resistance was evidenced by the prompt rise in pulmonary arterial pressure (from 22 to 130 per cent) and fall in pulmonary venous flow. (In this instance, pulmonary vascular resistance rose 100 per cent.)

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 &mu;g./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 dose range 20 to 47 &mu;g./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 &mu;g./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 occur in the systemic circulation. Pulmonary injection volumes never exceeded 1 ml. An immediate increase in pulmonary vascular resistance was evidenced by the prompt rise in pulmonary arterial pressure (from 22 to 130 per cent) and fall in pulmonary venous flow. (In this instance, pulmonary vascular resistance rose 100 per cent.)

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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, L81 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.; L81, 0.4 mg./Kg. and brom-LSD, 0.6 mg./Kg.

Duration of effect of antiserotonin substances was not studied systematically. Chlorprophenpyridamine, tripelennamine, tolazoline and reserpine were all without antisemtonin 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 volume,13 elevated left atrial pressure,11 or altered bronchomotor tone.11,16 In our laboratory and others,11,17,18 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,18 which demonstrated the by guest on July 9, 2017 http://circres.ahajournals.org/ Downloaded from...
Direct pulmonary vascular effects of serotonin. This was considered a possible mechanism for the results observed in this study, but further investigation is needed to confirm this hypothesis.

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Prornethazine, 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 INTERLINGUA

Le effectos que serotonina exerce super le vasculatura pulmonar de canes intacte esseva studiate in un experimento in que le droga poteva esser excludite temporarimente ab le circulation systemic. Inter le agentes studiate, serotonina esseva le plus potente constrictor del vasos sanguinee pulmonar. Illo differeva ab altere vasoconstrictores pulmonar in tanto que per exemplo illo non evocava simultaneamente le grado de bronchoconstriction que resulta del uso de acetylcholina e histamina. Refluxos vascular systemic non se manifes-tava post le uso de serotonina in un preparato experimental in que tal reflexos haberea essite facile a demonstrar. Le reproducibilitate del effecto quando le substantia esseva administrate a intervallos de al minus 5 minutas permitteva le investigation de antagonismos phannacologic a serotonina in le pulmones. In iste respeeto, promethazina, diethylamido de acido lysergic, e le derivato 2-bromic de illo esseva le plus potente agentes studiate.

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