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 the 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.

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 6 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 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.

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FIG. 1. Original record of injection of 20 μg 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 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 μg/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, serotonin was present in the systemic circulation at B, but it was excluded from the systemic circulation at C. 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 a whole because of the variety of effects produced by different doses of serotonin. Injections of 0.5 to 10 μg/Kg. produced increases in pulmonary vascular resistance of 5 to 100 per cent. However, the doses of serotonin that produced increases in pulmonary vascular resistance were not altered by bilateral cervical vagotomy in 2 dogs.

Simultaneous Systemic Effects. Figure 1 demonstrates that while serotonin is confined only to the lungs, no simultaneous alterations occur in the systemic circulation. Pulmonary responses to serotonin were not altered by bilateral cervical vagotomy in 2 dogs.
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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, LSI) and brom-LSD were approximately equally active in antiserotin 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 HAS was 1.8 mg./Kg. Duration of effect of antiserotin substances was not studied systematically. Chlorprophenpyridamine, tripelennamine, tolazoline and reserpine were all without antisertin 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, 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 the involvement of the pulmonary vasculature in the response to hypoxia and increased sympathetic tone.

The pulmonary vasculature responds to changes in blood flow by altering pulmonary vascular resistance. This response is mediated by local production of vasoactive substances, such as serotonin, which is released from platelets and other cells in response to injury or inflammation. The magnitude of this response appears to be influenced by the concentration of serotonin, the rate of release, and the local environment. In this study, we demonstrated that the administration of serotonin resulted in an increase in pulmonary vascular resistance, which was not blocked by the administration of a serotonin antagonist.

In conclusion, our study suggests that serotonin plays a role in the regulation of pulmonary vascular resistance. Further research is needed to elucidate the mechanisms by which serotonin affects the pulmonary vasculature and to determine the clinical implications of these findings.
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 used in previous studies. Histamine also 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. The present study shows that this effect in response to serotonin is slight and inconstant. 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.

Many investigators are studying serotonin antagonists, especially in their relationships to brain function. Konzett has shown antagonism of LSD-25 and brom-LSD against the bronchoconstrictor effects of serotonin in cats and guinea pigs. In the present study, the antiserotonin property of promethazine is noteworthy. This effect was noted in the systemic circulation by Gyennek, Lazar and Csak. Another phenothiazine derivative, chlorpromazine, is a particularly potent serotonin antagonist, and phenothiazine derivatives in general are emerging as a class of drugs worthy of special study in this regard.}

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 least 5 min. intervals permitted investigation of pharmacologic antagonism to serotonin in this preparation.
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Prornethazine, lysergic acid diethylamide and its 2-brorn 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. Proe. 17: 88, 1955). Knisely and his colleagues suggest that increased pulmonary vascular resistance due to serotonin may be due, in whole or in part, to transient embolization.

REFERENCES


The effectos que serotonina exerce super le vaseulatura 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 simultaneemente le grado de bronchoconstriction que resulta del uso de acetylcholina e histamina.

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