Pulmonary Vascular Responses to Serotonin and Effects of Certain Serotonin Antagonists

By JOHN C. ROSE, M.D. AND ERIC J. LAZARO, M.D.

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.

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 g./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 determined.

Received for publication December 21, 1957.
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 the group of 66 and 128 recordings, increases of 66 and 128 per cent were not observed by bilateral carotid occlusion. Pulmonary vascular resistance was increased in an average of 50 per cent at a mean of 60 seconds after the injection. In 128 recordings, increments of 60 to 120 per cent (mean 65 per cent, 10 to 15 seconds after the injection) were made. The same increase of 6 to 120 per cent (mean 62 per cent, 5 to 15 seconds after the injection) was made in the pulmonary arterial resistance increase of 6 to 120 per cent (mean 62 per cent, 5 to 15 seconds after the injection). Pulmonary systemic vascular responses were made in the pulmonary arterial pressure. 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.

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 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, 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, as illustrated by the following data. In the dose range 1.5 to 8.5 μg/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 μg/Kg. 15 injections were made resulting in increases of 22 to 130 per cent (mean 62 per cent, S.D. ± 36). Two injections of 80 μg/Kg. caused increases of 66 and 122 per cent.

In the group of 66 and 128 recordings, flow and pressure responses to serotonin were observed. During the period in which the left atrial tube was diverted from the pulmonary circulation were observed. During the period in which the left atrial tube was diverted from the pulmonary circulation were observed. During the period in which the left atrial tube was diverted from the pulmonary circulation were observed. During the period in which the left atrial tube was diverted from the pulmonary circulation were observed.
Discusison

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 factors such as 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 vaso motor activity. Notable in this regard are the recent studies of Borst, Berglund and McGregor, which demonstrated the by guest on July 9, 2017. http://circres.ahajournals.org/ Downloaded from
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 far lower than those of acetylcholine19 and epinephrine and norepinephrine 11 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.16 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. 18

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,19 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, 20 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. This was considered a possible mechanism. Thus was presented a possible mechanism. This was considered a possible

**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 the pulmonary vasculature.
SEROTONIN, ANTAGONISTS AND LUNGS

The effects that serotonin exerts on the pulmonary vasculature 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 vessels. It differed from other pulmonary vasoconstrictors in that, for example, it did not produce the degree of bronchoconstriction that results from the use of acetylcholine and histamine. No reflex vasoconstriction was noted after the use of serotonin in an experimental preparation in which reflexes had been shown to be easy to demonstrate. The reproducibility of the effect when the substance was administered at intervals of 5 minutes permitted the investigation of pharmacologic antagonism to serotonin in the lungs. In this respect, promethazine, diethylamide of lysergic acid 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, brom-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.

REFERENCES


In conclusion, serotonin is a potent pulmonary constrictor in the dog, whose effects are potentiated by drugs and diminished by bromide.

ACKNOWLEDGMENTS

Potential conflicts of interest for this article: none declared.

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 simultaneemente le grado de bronchoconstriction que resulta del uso de acetylcholine e histamina. Reflexos 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 ad-ministrate 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.


Pulmonary Vascular Responses to Serotonin and Effects of Certain Serotonin Antagonists

JOHN C. ROSE and ERIC J. TAZARO

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
Copyright © 1958 American Heart Association, Inc. All rights reserved.
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:
http://circres.ahajournals.org/content/6/3/283

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/