Action of histamine and H<sub>1</sub> and H<sub>2</sub> blockers on the cardiopulmonary circulation

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IN A PREVIOUS REPORT, we showed that in the chronically instrumented nonpregnant sheep the action of histamine on the regional circulation depended on its route of administration (24). When given intravenously, histamine produced a hypotension and tachycardia along with a decrease in iliac and uterine blood flows. When injected intra-arterially, however, histamine produced an increase in these same regional blood flows without changes in blood pressure. These contrasting peripheral circulatory responses to histamine could be blunted with H<sub>2</sub> receptor blocking agents. On the basis of these results, we postulated that the regional circulatory response to histamine depended on: a) whether or not there are concomitant central hemodynamic alterations, and b) the type of receptors and their distribution in the heart and the different vascular beds (24).

Most of the studies on the changes in central hemodynamics produced by histamine seem to indicate an increased pulmonary vascular resistance and a decreased cardiac output (1, 2, 4, 7, 10, 12, 14, 24, 25). Recently, however, Tucker and co-workers (21) showed a transitory increase in cardiac output during histamine infusion in anesthetized dogs.

The present report deals with data on the central hemodynamic effects of histamine when administered intravenously or directly into the pulmonary artery of the nonpregnant chronically instrumented unanesthetized sheep. The studies include observations on the effects of blocking the H<sub>1</sub> and H<sub>2</sub> receptors as well as the neural impulses at the autonomic ganglia on the histamine-induced cardiovascular alterations.

MATERIALS AND METHODS

Six young, healthy, adult nonpregnant ewes of mixed breed were selected for the study. Under local anesthesia and aseptic technique, one polyvinyl catheter was placed in the carotid artery for systemic blood pressure monitoring and for collection of blood samples, and another one into the jugular vein for drug administration. A catheter was placed in the main pulmonary artery through the femoral vein, and its final location established by the pressure pattern recorded on the Dynograph and, after termination of the experiment, by autopsy. Two of the six animals were selected for cardiac output measurements by the electromagnetic method used in the regional blood flow studies previously reported. The surgical procedure was as follows. Under general halothane anesthesia and sterile technique, one polyvinyl catheter was placed in the main pulmonary artery through the femoral vein, and its final location established by the pressure pattern recorded on the Dynograph and, after termination of the experiment, by autopsy. Two of the six animals were selected for cardiac output measurements by the electromagnetic method used in the regional blood flow studies previously reported. The surgical procedure was as follows. Under general halothane anesthesia and sterile technique, the left fourth intercostal space was entered. The pericardial sac was opened and the main pulmonary artery was identified and isolated. A cuff-type electromagnetic flow transducer of the type described elsewhere (23) was selected to fit around the main pulmonary artery without exerting undue constriction. After implantation of the transducer, the pericardial sac was closed and the leads of the flow probe brought out the chest and through a subcutaneous tunnel onto the back of the animal. Intrathoracic negative pressure was reestablished by standard techniques. A postoperative recovery period of 4 days was allowed before testing was begun. In addition to these measurements, cardiac output changes were measured in one animal during repeated
tests with intravenous infusion of histamine, using the dye dilution technique as previously reported (17).

**Testing protocol.** The testing of histamine and its blockers was carried out as follows. Each animal was allowed to rest quietly in its cage for 30 min prior to the onset of drug administration. During this period, baseline pulmonary blood flow and pulmonary and systemic arterial pressures, as well as heart rate, were continuously recorded while blood respiratory gases and pH were analyzed 2 or 3 times. A standard dose of 0.5 μg/kg of histamine base was then administered as a bolus injection, either intravenously or into the pulmonary artery; flow and pressures were recorded continuously until they returned to control values. The effects of this dose in a given animal were tested up to 3 times; an adequate interval was allowed between subsequent tests for all parameters to stabilize at control levels. In the animal given histamine infusion, the dose was 10 μg/kg per min for 5 min. Cardiac output was measured 5 or 6 times before, during, and at 15 and 30 min after the cessation of the infusion.

To test the influence of blocking the H₁ and H₂ receptors, as well as the autonomic ganglia, on the histamine action, the standard test of histamine was first performed and its circulating effects established. The animal was then primed with either 0.5 mg/kg diphenhydramine (Benadryl) or 1 mg/kg metiamide and the effects of the same histamine dose were repeated. Ganglionic blockade was accomplished with an intravenous infusion of trimethaphan camphorsulfonate (Arfonad), 100 μg/kg per min for 15-20 min. Studies in our laboratory have shown that complete blockade of the stimulating action of 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) is accomplished in nonpregnant and pregnant ewes when this agent is administered (17, 22, 26). Blood flow, pressures, blood respiratory gases, and pH were monitored and recorded by techniques previously described (3, 15).

**RESULTS**

**Animal condition.** All animals included in the present study were healthy and were tested no sooner than 4 days following surgery. Their cardiovascular functions and blood respiratory gases were within the range previously reported in our laboratory for unanesthetized sheep (3).

**Effects of intravenous histamine administration.** Figure 1 illustrates a typical example of the response of the heart rate (HR), systemic arterial pressure (AP), pulmonary artery pressure (PAP), and pulmonary artery flow (PAQ) to a single intravenous injection of 0.5 μg/kg of histamine. About 8 s after the injection, the systemic arterial pressure began to fall, the systolic more than the diastolic, and by 30-35 s the pressure had returned to or slightly higher than control values. The heart rate increased significantly during the systemic hypotensive phase and returned to control thereafter. Pulmonary arterial pressure (both phasic and mean) increased, and pulmonary blood flow decreased significantly for about 2 min after histamine injection (Fig. 1); these changes reflected a rise in pulmonary vascular resistance.

Figure 2 compares the effects of histamine in one animal tested in the unanesthetized condition and after it had been anesthetized with pentobarbital (12 mg/kg). Before the anesthesia, histamine produced the typical response described above. Pentobarbital administration per se produced insignificant changes in the systemic and pulmonary vascular pressures and pulmonary blood flow. Histamine injection at the height of anesthesia elicited an insignificant increase in the pulmonary ar-
Central hemodynamic action of histamine

Figure 2. Example of effects of pentobarbital anesthesia on the pulmonary circulatory response to intravenous histamine. Note marked alteration of pulmonary hypertension and reversal in pulmonary blood flow produced by histamine when animal was under pentobarbital anesthesia.

Figure 3. Changes in heart rate, systemic arterial and pulmonary arterial pressures produced by histamine before and after blockade of H1 and H2 receptors and autonomic ganglia. Values represent percent change from control ± 1 SE. (n, number of tests.) Although difference between effects produced by intravenous injection of histamine alone and those observed after various blockades was significant (for more details, see text).

Pretreating the animal with 0.5 mg/kg of Benadryl elicited an average increase of 45% in heart rate, a 15% decrease in mean arterial pressure, and a 26% increase in pulmonary artery pressure and flow did not change significantly. The changes after Arfonad in the pulmonary pressure and heart rate changes were of borderline significance. The statistical analyses further showed that the differences between the actions of the three forms of blockade were not significant when compared to each other.

Intravenous infusion of 10 μg/kg per min of histamine elicited a strong initial (1-2 min) reaction during which the animal became restless and had breathing difficulties that made measurement of the cardiac output somewhat difficult. When the animal became quiet, the arterial pressure and cardiac output exhibited a marked fall, whereas the heart rate increased during histamine infusion (Table 1). The decrease in cardiac output and arterial pressure outlasted the duration of infusion.

Effects of intrapulmonary arterial administration of histamine. Figure 4 presents a typical example of the effects of injecting 0.5 μg/kg of histamine into the main pulmonary artery, and Fig. 5 compares the average changes produced by intravenous and intrapulmonary artery injections. In contrast to intravenous administration, injection of histamine directly into the pulmonary artery failed to change the pulmonary artery pressure and blood flow appreciably. The same negative effects were observed in neonatal lambs when histamine was injected into the pulmonary artery (unpublished data).
PULMONARY ARTERY
HISTAMINE (0.2 μg/kg)
Sheep 7C74
Wt. 30 kg

**FIG. 4.** Illustrative example of effects of histamine injection into pulmonary artery. Note absence of any significant alterations in arterial and pulmonary artery pressures as well as in pulmonary artery flow and heart rate.

**DISCUSSION**

The cardiovascular effects of exogenously administered histamine have been investigated in adult, fetal, and neonatal animals, with and without anesthesia, as well as in isolated lung and heart preparations (1, 2, 5, 7, 10, 14, 16, 19-21, 24, 25). The results have been inconsistent and have depended on the animal species, age, the condition of the experimental model, including the anesthesia, and the dose and route of histamine administration.

In the adult and neonatal animal, whose pulmonary vascular resistance in the resting state is low, intravenous histamine usually produces pulmonary vasoconstriction, systemic hypotension, and a decrease in the cardiac output (1, 14, 24, 25). To our knowledge, the only exception to this hemodynamic response is the observation of Tucker et al. (21) in anesthetized dogs wherein a transient increase in cardiac output was observed during infusion of relatively large doses of histamine.

In the fetal lamb whose resting pulmonary vascular resistance is relatively high, histamine produces a fall in pulmonary vascular resistance and pressure (6, 25).

The mechanisms of action of histamine on the cardiovascular system are controversial. The tachycardia has been attributed to stimulation of the H₂ histamine receptor in the right atrium, since it can be successfully antagonized by the H₂ blocking agents burimamide and metiamide (13, 16, 24). The pulmonary hypertension is thought to be related to pulmonary venous constriction; this latter response leads to increased pulmonary vascular resistance, decreased ventricular filling, and a fall in the cardiac output (1, 24). The systemic hypotension would then be secondary to the decreased cardiac output. Others, however, believe that the systemic hypotension is secondary to a peripheral vasodilatation (19, 21).

The hypothesis of increased pulmonary vascular resistance with secondary reduction in ventricular filling

<table>
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<tr>
<th>Time, min</th>
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<th>Arterial Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>Cardiac Output, ml/min per kg</th>
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<td>14</td>
<td>100 ± 1.6</td>
<td>72 ± 1.4</td>
<td>110 ± 5.5</td>
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<td>Histamine, 10 μg/kg per min for 5 min</td>
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n, number of measurements.

**FIG. 5.** Comparison of changes in circulatory parameters produced by same dose of histamine when injected intravenously or directly into pulmonary artery. Values are means of number of tests (n) ± 1 SE. Note marked difference between the two routes of administration.
is supported by studies on isolated lung preparations that demonstrated pulmonary venous constriction following histamine administration (5, 7, 10-12, 14). Additional support is provided by in vivo observations of reduced regional blood flows after intravenous administration of histamine (1, 24).

The present data obtained from unanesthetized, chronically instrumented sheep provide clear evidence of the pulmonary vasoconstrictive action of histamine when this agent is administered intravenously. The decrease in pulmonary blood flow that was evident when measured either with flow transducer or with dye dilution technique supports the concept that these central hemodynamic changes represent the primary factor responsible for the fall in systemic arterial pressure and regional blood flows observed by us and by others after intravenous administration of histamine (1, 24). The suppression of the histamine-induced pulmonary hypertension and the reversal of its action on the cardiac output by pentobarbital may explain the findings of Tucker and co-workers (21) in anesthetized dogs. These findings are consistent with our previous studies in which pentobarbital anesthesia alters the cardiovascular responses to vasoactive compounds such as angiotensin, hydralazine, and ganglionic stimulation (3, 18). Although the exact mechanisms by which pentobarbital anesthesia alters the response to vasoactive agents are not known, they probably include action on the neurohumoral control of the circulatory system as well as a direct effect on vascular smooth muscle tone.

The absence of any significant action on the pulmonary vascular bed of the intact, unanesthetized animal when histamine was injected directly into the pulmonary artery is rather puzzling. Numerous reports have shown that in isolated perfused lung preparations of anesthetized animals, histamine produces strong pulmonary venous constriction (7, 10-12). Whether these differing results are related to the anesthesia or to any other aspect of the perfused preparation cannot be stated at this time. At any rate, this striking difference in the pulmonary action of histamine between the intact unanesthetized animal and the perfused preparation becomes even more intriguing when one attempts to attach a given circulatory response to stimulation or inhibition of a given receptor.

It is clear from the present data that the histamine-induced tachycardia may be mediated through either the H_{1} or H_{2} receptors, or both, since blockade of these receptors results in a near-equal attenuation of the heart rate increase. This absence of any specific receptor action is even more evident when one considers the response of the pulmonary artery pressure. As Fig. 3 shows, the magnitude of the blunting action of Benadryl (H_{1} blocker) on the histamine-induced pulmonary hypertension is not significantly different from that produced by metiamide (H_{2} blocker). Hence, it is difficult to attribute the pulmonary vascular action of histamine to either of these two receptors alone. These findings leave us with the possibility that a) when histamine enters the systemic venous circulation, it stimulates both these receptors simultaneously, or b) in the cardiovascular system of the unanesthetized sheep, unlike that of the anesthetized dog, there is no specific circulatory action that could be strictly related to a given histamine receptor.

Regardless of the interrelationship of receptor-circulatory function, the absence of any pulmonary vascular effect when histamine was injected directly into the pulmonary artery seems to suggest that the right side of the heart is necessary for histamine to exert its circulatory action, at least in the intact, unanesthetized animal. These findings lead us to believe that a) the primary site of histamine receptors in the heart is either the right atrium or the right ventricle, b) whatever other receptors that exist in the pulmonary vascular bed may not be essential for the full circulatory manifestations of histamine, and c) a neural reflex mechanism may be involved in the overall circulatory action of histamine.

The interrelationship between histamine and the autonomic nervous system is rather complex and the net results depend on many variables, such as animal species, type of experimental preparation, the functional status of the adrenosympathetic system, and so forth (8, 9). It is generally agreed, however, that under certain circumstances histamine may release catecholamines from the adrenals and other chromaffin tissues and that some of its secondary circulatory manifestations may be related to such an action (8). In addition, certain histamine actions may be mediated through the autonomic nervous system. Using isolated atrial guinea pig preparations, von Euler (9) observed that the characteristic histamine action may vanish if the preparation is exposed to the ganglionic blocker hexamethonium for a sufficient time.

Our present observations on the magnitude of the histamine-induced cardioacceleration and pulmonary hypertension before and after ganglionic blockade with Arfonad provide further evidence to support von Euler's findings. In every instance, blockade of the neural traffic at the ganglionic level attenuated but did not totally abolish the histamine-induced tachycardia and pulmonary hypertension. These findings suggest strongly that at least some aspects of histamine action on the circulation may involve a neural reflex. The fact that blockade of the neural transmission at the ganglionic level did not totally abolish the cardiovascular effect of histamine suggests that more than one site and mechanism of action exists for mediating the response to this agent.

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