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Action of Histamine and its Receptor Blockers on Uterine Circulation in Sheep[1] (39313)

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The role of histamine in regulating systemic and regional hemodynamics has intrigued investigators ever since the first report of Dale and Laidlaw (1) on the anaphylactic-like effects of its administration. The recently developed concept of Black *et al.* (6) of dual histamine receptors has allowed a better understanding of this substance as a mediator of physiological and pharmacological responses.

Earlier confusion regarding mechanisms of histamine action stemmed from the inability of the available antihistaminic agents to block all of the known responses to histamine administration. In 1972, burimamide, the prototype of a new class of antihistaminic agents was introduced. Animal studies using this and similar agents led to the conclusion that there are two histaminic receptors, designated H_1 and H_2. Cardiovascular functions related to H_1 receptor have been identified in the A-V node of the heart (2), pulmonary veins (3, 4) and bronchial smooth muscles (3, 5), whereas H_2 receptors are thought to be located in the right atrium (2, 6). The distribution of these receptors in the peripheral vascular beds is less well defined, but it is believed that they may play a role in the regulation of regional vasomotor tone (7, 8).

The present study was designed to investigate the uterine hemodynamic response to histamine in terms of activities of H_1 and H_2 receptors. The behavior of the iliac vascular bed during these studies served for comparison.

Methods and materials. Experiments were carried out on nonpregnant ewes chronically instrumented for measurements of uterine and iliac blood flows and arterial pressure by techniques previously reported (9, 10). Polyvinyl catheters were placed in the jugular vein for drug administration and in the carotid artery for arterial pressure recordings and for arterial blood sampling. Electromagnetic flow transducers were placed on the common uterine artery near its exit from the aorta to measure total uterine blood flow; another flow transducer was placed around an external iliac artery to monitor its blood flow.

In some animals, effects of intra-arterial (ia) injections of drugs were investigated by injecting them through a small catheter placed above the aortic bifurcation through a branch of the external iliac artery, contralateral to the iliac flow probe. This approach allowed drug administration to uterus and lower extremities simultaneously and permitted observations of the histamine response in these two parallel vascular beds.

The experimental protocol was comprised of the following steps:

(A) A control period lasting 30 min, during which arterial pressure and uterine and iliac blood flows were recorded continuously while the animal was standing still in its cage. Blood respiratory gases were analyzed once or twice during this period.

(B) A drug administration period during which progressively increasing doses of histamine were injected iv or ia while the pressure and flows were recorded continuously. Histamine doses were expressed in terms of the base and were administered in 1 ml over 15 sec. Frequently, effects of a given dose were tested two to six times in the same animal. An adequate interval was allowed between subsequent injections for pressures and flows to return to preinjection levels.

Histamine blockers used were diphenhydramine (Benadryl, Parke, Davis and Co.,

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Detroit, Mich.) for the H_1 and metiamide (Smith Kline & French Laboratories, Philadelphia, Pa.) for the H_2 receptors. Benadryl was administered in a 1-cc volume over 15 sec. Metiamide, on the other hand, was infused in a 20-cc volume over a period of 10 min. This route of metiamide administration was arbitrarily chosen because of lack of information concerning dosage and method of administration in the ewe.

(C) A recovery period was allowed after each drug administration, during which flows and pressures were recorded until they returned to control values.

Pressures, flows, and blood respiratory gases were recorded by techniques previously reported (9, 10).

Results. (A) Animal condition. All animals used in this study were healthy and were tested no sooner than 4 days after they had recovered from surgery. Their cardiovascular functions and blood respiratory gases were within the range previously reported (10).

(B) Effects of iv administration of histamine. Figure 1 illustrates the composite responses of mean arterial blood pressure, heart rate, and total uterine and right iliac blood flows to 12 tests using iv injections of 0.5 μg/kg histamine in three animals. Mean arterial pressure fell by an average of 16% about 30 sec after injection; uterine and iliac blood flows decreased concomittantly by an average of 21 and 29%, respectively, whereas heart rate increased (Fig. 1). These changes were followed by a rebound phenomenon during which arterial pressure and uterine blood flow rose to levels higher than control (Fig. 1).

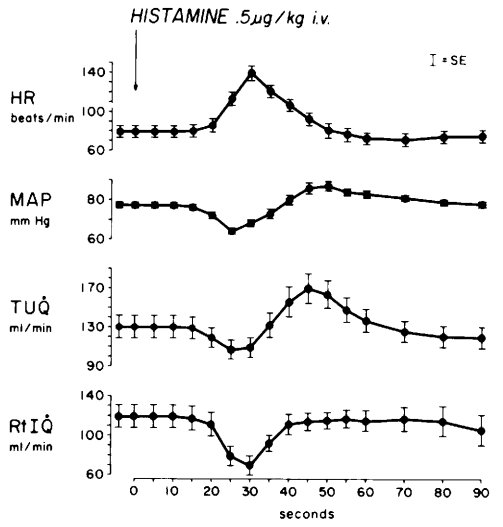

FIG. 1. Effects of iv histamine on heart rate (HR). mean systemic arterial presure (MAP), total uterine blood flow (TUQ̇), and right iliac blood flow (RTIQ̇); values are mean ± 1 SEM. Note increase in HR and simultaneous decrease in arterial pressure and blood flows. Rebound in MAP and flows is evident.

Figure 2 illustrates an example of the effects of iv administration of histamine and its specific receptor blocking agents on phasic arterial pressure. The hypotension produced by histamine was more pronounced on systolic than diastolic pressure. During the rebound phenomenon, both systolic and diastolic pressures increased equally above control values.

Administration of 0.25 mg/kg of Benadryl prior to histamine injections abolished the hypotensive and positive chronotropic effects of histamine immediately. This antagonism lasted for about 1 hr.

When the animal was primed with 0.5 mg/kg of metiamide iv, the same dose of histamine produced the typical hypotensive effect but no increase in heart rate (Fig. 2).

(C) Effects of ia administration of histamine. Figure 3 illustrates the phasic responses of arterial pressure and iliac and uterine blood flows to ia injections of 0.02 to 0.5 μg/kg of histamine; Fig. 4 presents mean changes in uterine flow and vascular resistance after four to eight injections at each dose level. Intra-arterial injections of histamine produced consistent increase in uterine blood flow and decrease in uterine vascular resistance which were dose-dependent; iliac blood flow also increased but systemic arterial pressure and heart rate were not altered (Fig. 3).

To test the role of the beta adrenergic receptors in the histamine-induced vasodilatation, isoproterenol injections were given before and after Benadryl. Blockade of H_1 receptors had no influence on the beta receptor mediated uterine vasodilatation.

Figure 5 shows the effects in three animals of repeated ia injections of 0.2 μg/kg histamine over a period of 90 min on uterine and iliac blood flows before and after Ben-

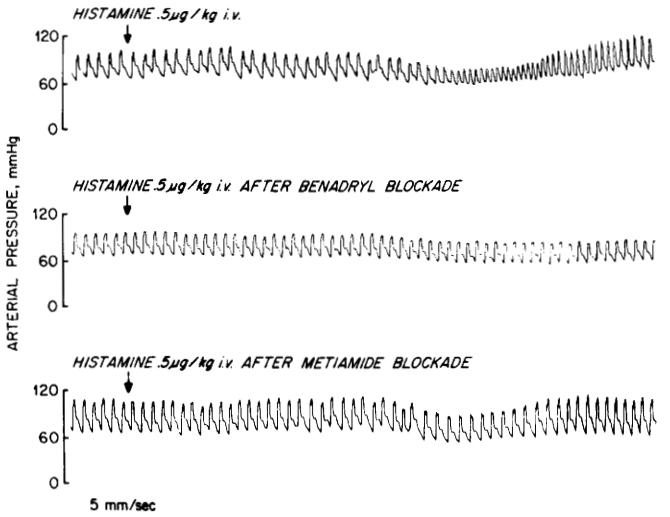

FIG. 2. Effects of iv histamine on phasic arterial pressure before and after administration of H_1 blocker (Benadryl, 0.25 mg/kg) and H_2 blocker (metiamide, 0.5 mg/kg). Pressure and HR changes were blocked by administration of H_1 blocker; H_2 blocker abolished the tachycardia but not the hypotension.

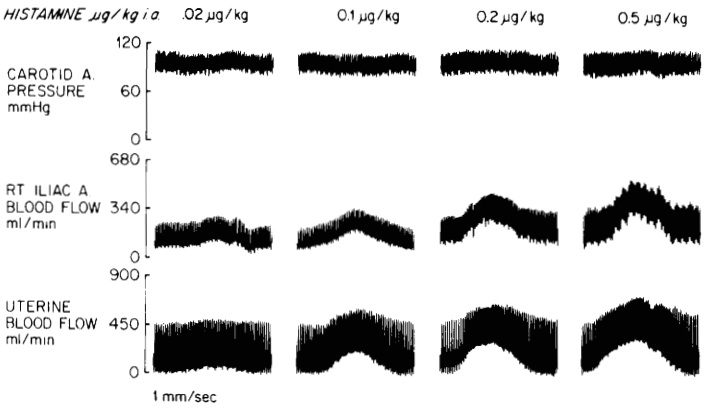

FIG. 3. Segments of a record depicting effects of different doses of histamine injected ia on phasic systemic arterial pressure and uterine and iliac blood flows. Note absence of any effect on carotid arterial pressure. Iliac and uterine blood flows increased with each injection and the increment was dose-related.

adryl and metiamide administration. Each observation represents four to eight injections. The magnitude of response of uterine blood flow to the same dose of histamine decreased with time, suggesting tachyphylaxis. This pattern, however, was not evident in iliac flow.

Intra-arterial administration of Benadryl decreased the response to histamine for only the first 10 min, whereas metiamide did not alter the response to repeated histamine injections.

Discussion. The systemic response in the nonpregnant, unanesthetized ewe to iv histamine observed in the present study is in agreement with the observations of Alexander and Halmagyi in the unanesthetized ewe and consist primarily of tachycardia and systemic hypotension (3, 4, 11). These authors thought that the histamine induced hypotension was probably secondary to a decrease in the cardiac output. This hypothesis receives some support from our data which showed a greater decrease in the systolic than diastolic pressure and a concomittant fall in uterine and iliac blood flows following iv histamine administration. The mechanisms by which histamine decreases

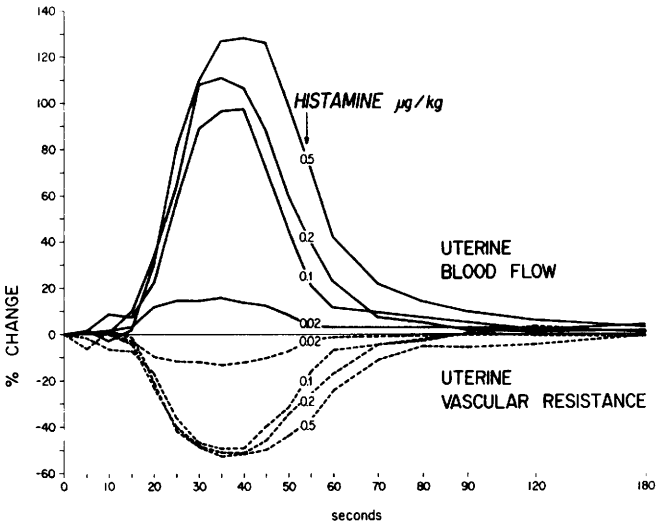

FIG. 4. Uterine blood flow and vascular resistance changes (percentage from control) after different doses of histamine injected ia; each dose was taken from four to eight times. Note the progressively increasing changes in flow and decreasing changes in vascular resistance which were dose-related.

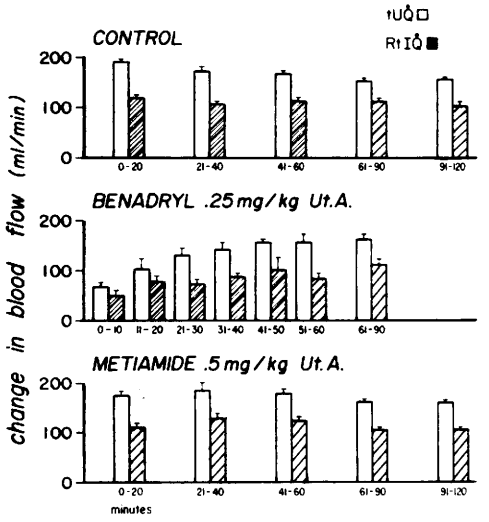

FIG. 5. Total uterine blood flow (TUQ) and right iliac blood flow (RTIQ) changes in three animals to repeated ia injection of 0.2 μg/kg histamine over a period of 90–120 min. Each observation represents four to eight histamine injections. Upper panel shows uterine blood flow (TUQ) response to the same dose of histamine decreases with time, whereas the iliac blood flow (RTIQ) response remains the same. Middle panel shows that following ia administration of 0.25 mg/kg Benadryl, response of uterine and iliac blood flows to same dose of histamine was most attenuated within the first 30 min. Pretreatment with ia metiamide, 0.5 mg/kg (lower panel), had no effect on histamine response in either vascular bed.

the cardiac output are not well understood. Pulmonary venous constriction and decreased left ventricular filling have been suggested (3). Other investigators have attributed this response to both peripheral dilation and impaired cardiac function (12).

The mechanisms of the rebound phenomenon during which the arterial pressure, as well as the uterine blood flow, rose to levels higher than those seen prior to histamine injections are difficult to explain. Emmelin and Muren demonstrated that histamine was capable of releasing adrenalin from the adrenal medulla (13). It is possible that the hypertensive phase seen during the rebound phenomenon is related to catecholamine release or to an overall adrenergic stimulation caused by baroreceptor response to the histamine induced hypotension. This hypothesis, however, does not explain the rebounding increase in uterine blood flow since adrenergic stimulation usually decreases the uterine flow (9). Further work is necessary to elucidate this question.

The observation that, following systemic Benadryl administration, the histamine-induced hypotension was markedly attenuated, suggests H_1 receptor as the principal mediator of this response. Benadryl was also observed to attenuate the tachycardia of systemic histamine administration. While

this might suggest H_1 receptor activity in the right atrium, a more likely explanation is based on the procaine-like cardiac effects of H_1 antihistamine agents (2, 14).

Histamine-induced tachycardia has been shown to be H_2 receptor mediated in several other animal species (2, 6, 15). This response in our studies occurred independently of beta adrenergic activity and was successfully blocked by the H_2 antihistamine, metiamide. Unlike the Benadryl blockade, which was immediate in onset, metiamide had a widely variable onset of activity, appearing from 10 min to 1 hr after administration.

When histamine was administered ia, a dose-dependent uterine and iliac vasodilatation occurred with an increase in blood flow and a decrease in the vascular resistance; the systemic arterial pressure was not affected. These changes are in marked contrast to those observed after iv administration of histamine. Similar findings after ia injections have been reported for other regional beds (3, 8, 12).

These results seem to suggest that physiologic or pathologic conditions that lead to histamine release in localized vascular regions may first be reflected by local vasodilatation and increased blood flow. But if histamine release continues and a sufficient amount reaches the systemic circulation, the effects on the cardiac output may overcome or mask the local effects and a decrease in blood flow instead of an increase may be observed.

The present data also show that following repeated histamine injections, the uterine vascular bed exhibited tachyphylaxis whereas the iliac bed did not. A precise explanation of these findings is not yet available.

Benadryl, administered ia attenuated the histamine response in both the uterine and iliac vascular beds. This blocking effect was most pronounced during the first 10 min after administration and was absent by 1 hr. The fact that isoproterenol induced vasodilatation was not influenced by Benadryl administration indicates that this H_1 antagonist does not block peripheral beta adrenergic receptors.

Finally, metiamide administered ia did not influence either the uterine or iliac histamine response. This would imply that there are no H_2 histamine receptors in these vascular beds and strongly negates its role as an active mediator of regional vasomotor tone in this model.

Summary. Effects of iv and ia administration of histamine and its H_1 and H_2 blockers (diphenhydramine and metiamide) on systemic arterial pressure, heart rate, and uterine and iliac blood flows were investigated in unanesthetized, chronically instrumented nonpregnant ewes.

Intravenous histamine produced tachycardia, hypotension, and decreased iliac and uterine blood flows. In contrast, ia injections produced a significant increase in blood flows in these vascular beds which was dose-dependent.

Evidence is presented to show that some of the circulatory actions of histamine may be related to stimulation of H_1 while others may be related to H_2 receptors. The peripheral circulatory action produced by iv histamine is probably secondary to its effects on reducing cardiac output. The uterine and iliac vascular beds contain mostly H_1 receptors since their response to histamine can be blocked almost totally by Benadryl and not by H_2 antagonist metiamide.

1. Dale, H. H., and Laidlaw, P. P., J. Physiol. (London) **52,** 355 (1919).
2. Levi, R., and Capurro, N., *in* "International Symposium on Histamine H_2 Receptor Antagonists," p. 175, London (1973).
3. Alexander, F., Eyre, P., and Head, K. W., J. Comp. Path. **77,** 1 (1967).
4. Halmagyi, D. F. J., Starzecki, B., and Horner, G. J., J. Appl. Physiol. **18,** 544 (1963).
5. Ash, A. S. F., and Schild, H. O., Brit. J. Pharmacol. **27,** 427 (1966).
6. Black, J. W., Duncan, W. A. M., Durant, G. J., Ganellin, C. R., and Parsons, M. E., Nature (London) **236,** 385 (1972).
7. Glover, W. E., Carroll, P. R., and Latt, N., *in* "International Symposium on Histamine H_2 Receptor Antagonists," p. 169, London (1973).
8. Parsons, M. E., and Owen, D. A. A., *in* "International Symposium on Histamine H_2 Receptor Antagonists," p. 127, London (1973).
9. Ladner, C., Brinkman, C. R. III, Weston, P., and Assali, N. S., Amer. J. Physiol. **218,** 257 (1970).
10. Assali, N. S., Brinkman, C. R. III, and Nuwayhid, B., Amer. J. Obstet. Gynecol. **120,** 411 (1974).

11. Alexander, F., Eyre, P., and Head, K. W., J. Comp. Path **80,** 19 (1970).
12. Powell, J. R., and Brody, M. J., *in* "International Symposium on Histamine H_2 Receptor Antagonists," p. 137 London (1973).
13. Emmelin, N., and Muren, H., Acta Physiol. Scand. **17,** 345 (1949).
14. "International Encyclopedia of Pharmacology & Therapeutics," Pergamon Press, New York (1973).
15. Hughes, M. J., and Coret, I. A., Proc. Soc. Exp. Biol. Med. **148,** 127 (1975).

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