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The Influence of Histamine and Serotonin in Promoting Early Uterine Growth in the Rat[1]

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Previous studies from these laboratories demonstrated that estrogen-induced histamine release, or histamine itself, may trigger the acute vasodilatation, hyperemia, and increase in capillary permeability which permit the accumulation of electrolytes, water and other metabolites in the stimulated target. These investigations have been extended to serotonin and heparin. Heparin was without effect 4 or 24 hr after intrauterine administration to adult ovariectomized rats. Serotonin, on the other hand, exhibited a striking similarity to histamine in its early influence on uterine vascularity and water imbibition, and was approximately 17 times as effective on a molar basis. Mitotic activity in the epithelium was conspicuous 24 hr after histamine treatment. Serotonin had a similar but less intense influence on epithelial mitoses. Intraluminally administered LSD-25 inhibited the hyperemia and water imbibition due to estrogen, even in adrenalectomized animals. Whether serotonin, which exhibits the estrogenicomimetic properties of histamine, normally functions in this capacity under circumstances associated with hormonal action remains to be determined.

INTRODUCTION

True growth of the uterus is established approximately 20 hr following a single intravenous injection of estrogen in the ovariectomized rat. This is preceded by, and may be dependent upon, earlier modifications of cellular composition and enzymatic activity (Szego and Roberts, 1953). The acute changes reach their peak at about 4 hr. These include a striking increase in vascularity of the organ associated with accumulation of water, electrolytes (Szego and Roberts, 1953; Roberts and Szego, 1953; Spaziani and Szego, 1958), and plasma proteins (Kalman, 1955).

On the basis of previous work from these laboratories (Spaziani and Szego, 1958, 1959), it has been proposed that the accumulation phenomena are secondary to the hyperemia and increased capillary permeability evoked by endogenous histamine or related substances released by estrogen. Other naturally occurring vasodilator agents were not excluded specifically from possible participation (Spaziani and Szego, 1959). Particular attention was drawn to serotonin because of its demonstrated role in promoting localized hyperemia and edema formation, especially in the rat (Rowley and Benditt, 1956; Sparrow and Wilhelm, 1957). Indeed, its release from specific sites often accompanies the depletion of histamine therefrom (cf. Page, 1958).

It is the purpose of the present report to test the effects of serotonin and some of its antagonists and of heparin, on uterine hyperemia and hydration. Heparin, along with serotonin (Benditt *et al.*, 1955), is present in substantial concentrations in rat mast cells which also contain histamine (Riley and West, 1953). The present ex-

[1] Aided by a research grant (CY-1488) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, and by Cancer Research Funds of the University of California.

periments confirm the effectiveness of histamine in inducing uterine changes following direct intraluminal instillation. Heparin is inert by these criteria. Serotonin, on the other hand, bears a striking similarity to histamine in its early (4 hr) influence on uterine vascularity and water imbibition. These two amines are also effective stimulators of uterine epithelial mitotic activity 24 hr after local application.

The data demonstrate, therefore, that at least two constituents of the mast cell, a unit which appears to undergo acute degranulation in the uterus following estrogen administration (Westin, 1955), have estrogenicomimetic effects on this organ. Studies on the effects of serotonin inhibitors on the early responsiveness of the uterus to estrogen itself are also reported.

METHODS AND MATERIALS

Adult female Sprague-Dawley rats, averaging three months of age and approximately 250 gm in weight at the time of experiment, were used. They were bilaterally ovariectomized 14 to 16 days before treatment. Administration of test substances was under light ether anesthesia by intravenous [I.V.] (Roberts and Szego, 1947) or by uterine intraluminal [I.L.] (Spaziani and Szego, 1959) routes as previously described. Concentrations of histamine and of serotonin are expressed in terms of the free substances. The aqueous solutions were prepared from histamine dihydrochloride and serotonin creatinine sulfate.[2] As a departure from the preceding study, these were partially neutralized (to pH 5.5 to 7.0) before injection. The osmolarity of the resultant solutions was equivalent to that of 1.8% or of 3.36% saline, respectively. NaCl solution of the appropriate concentration was used for control injections. Heparin dosage is given in mg of heparin sodium. Bilateral adrenalectomy was performed when indicated just prior to parenteral injections. Potential inhibitors were administered immediately before estrogen. Tissue samples were obtained under light ether anesthesia 4 or 24 hr after injection of test substances. Uterine horns were removed and analyzed for water content as previously described.

[2] LSD-25 (*D*-lysergic acid diethylamide), UML-491 (1-methyl *D*-lysergic acid butanolamide tartrate), and a portion of the serotonin creatinine sulfate used in these studies were the generous gift of Mr. Harry Althouse of Sandoz Pharmaceuticals, Sandoz Incorporated.

RESULTS

Intraluminal Injection of Test Substances: The Influence of the Manipulations Involved

The effects on uterine hydration of injecting 0.02 ml per horn of 0.9%, 1.8% and 3.36% NaCl solutions were observed (Table 1). The 1.8% saline solution was chosen in the present experiment because of its osmotic equivalence (0.305 *M*) to the nearly-neutralized 0.25 mg/0.02 ml serotonin and 0.54 mg/0.02 ml histamine solutions. The 3.36% saline, similarly, was considered the control solution for 1.0 mg/0.02 ml histamine.

It will be noted that 0.9% saline introduced by this route promoted a slight but significant degree of uterine edema when compared to uninjected uteri from castrate controls ($p < 0.001$). The sham procedures involving the standardized degree of trauma but no transfer of fluid intraluminally also induced approximately the same degree of edema. The introduction of 1.8% or 3.36% saline I.L., on the other hand, led to restoration of uterine water levels toward the control value. Thus, the slight edema resulting from the trauma of uterine horn manipulation is unaffected by 0.9% saline I.L. The injection of (hypertonic) 1.8% and 3.36% salt solutions, however, counteracted the inflammatory process and promoted a redistribution of fluid toward normal. These solutions do not appear to have this property unless "inflammation" is present. Thus, they did not depress initial base lines (cf. Table 1, Group I). However, the 1.8% saline counteracted to a slight but significant degree the water imbibition due to intravenously administered estrogen (Table 2). It is concluded that control of osmolarity of intraluminally injected test solutions is required. Table 2 further reveals that 0.9% saline coupled with intravenous estrogen treatment did not promote further edema (Group III

TABLE 1

INFLUENCE OF INTRALUMINALLY INJECTED SALINE SOLUTIONS ON UTERINE WATER CONCENTRATION OF OVARIECTOMIZED RATS

Group	Description	Number animals	% H_2O[a]	"P"	Compared with group number
I	Uninjected controls	12	78.6 ± 0.19	—	—
II	0.9% saline[b]	11	80.6 ± 0.32	<0.001	I
III	Sham	5	81.6 ± 0.16	<0.001	I
IV	1.8% saline[b]	7	79.7 ± 0.33	0.01	I
				0.05	II
				<0.001	III
V	3.36% saline[b]	6	79.7 ± 0.63	0.2	I

[a] Deviations shown are S.E.M.
[b] Where indicated, solutions were administered intraluminally in the amount of 0.02 ml/horn.

TABLE 2

INFLUENCE OF UTERINE TRAUMA ON THE SUBSEQUENT WATER IMBIBITION RESPONSE TO ESTROGEN[a]

Group	Description	Number animals	% H_2O[b]	"P"	Compared with group number
I	Uninjected controls	12	78.6 ± 0.19	—	—
II	Estradiol-17β, 0.5μg/100 gm B.W.[c], I.V.[c]	9	85.2 ± 0.19	<0.001	I
III	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 0.9% saline I.L.[c]	5	84.4 ± 0.31	>0.05, <0.1	II
IV	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; sham I.L.	6	83.7 ± 0.63	>0.3	III
V	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; adrx.[c]; 0.9% saline I.L.	4	84.3 ± 0.31	0.8	III
VI	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 1.8% saline I.L.	8	83.6 ± 0.23	>0.05, <0.1	III
				<0.001	II

[a] Routes of injection are as indicated in body of Table. Volumes of all I.L. injections constant at 0.02 ml/horn.
[b] Deviations shown are S.E.M.
[c] B.W. = body weight;
I.V. = intravenous injection;
I.L. = intraluminal injection;
Adrx. = bilaterally adrenalectomized.

versus II) under conditions of apparently maximal water imbibition due to estrogen administration, even in the absence of the adrenals (Group V versus III).

ACUTE EFFECTS OF HISTAMINE, SEROTONIN AND HEPARIN

Table 3 represents the results obtained 4 hr following intraluminal application of histamine, serotonin, and heparin solutions. The influence of I.L. estradiol in the equivalent of twice-normal saline is also shown, as are the effects of appropriate control solutions. Table 3 confirms the earlier report that histamine can induce edema in the uterus of the adult ovariectomized rat (Spaziani and Szego, 1959). The maximal hydration achieved by the 1 mg/horn dose was statistically significant when compared to the 3.36% (osmolar

TABLE 3
EFFECTS OF MAST CELL CONSTITUENTS ON UTERINE WATER CONCENTRATION OF OVARIECTOMIZED RATS[a]

Group	Description	Number animals	% H_2O[b]	"P"	Compared with group number
I	Uninjected controls	12	78.6 ± 0.19	—	—
II	1.8% saline	7	79.7 ± 0.33	0.01	I
III	3.36% saline	6	79.7 ± 0.63	0.2	I
IV	Histamine, 1 mg	16	83.3 ± 0.40	<0.001	III
V	Histamine, 0.54 mg	4	82.0 ± 0.26	<0.001	II
				>0.01, <0.02	IV
VI	Serotonin, 0.25 mg	19	84.4 ± 0.38	<0.001	II
VII	Serotonin, 0.1 mg	7	83.1 ± 0.40	0.02	VI
VIII	Heparin, 3 mg[c]	5	79.9 ± 0.67	0.8	II
				>0.8	III
IX	Estradiol-17β, 0.1μg[d]	3	83.3	—	—

[a] All solutions administered intraluminally in the amount of 0.02 ml/horn. Dosages are indicated per horn.
[b] Deviations shown are S.E.$_M$.
[c] Molecular weight, hence osmolarity uncertain.
[d] Final osmolarity $\cong$ 1.8% saline.

equivalent) control. Likewise, 0.54 mg histamine/horn clearly stimulated uterine water imbibition.

Serotonin has similar estrogenicomimetic effects (Table 3). Its I.L. injection in the amount of 0.25 mg/horn yielded a statistically significant increase in uterine hydration ($p < 0.001$ versus its osmolar equivalent control, Group II). At a dose of 0.1 mg/horn the effect of serotonin was just inframaximal; at half this dosage (not shown in Table 3) there was definite evidence of edema but at a reduced level. Using the data in Table 3 as a rough guide and converting to a molar basis, it may be judged that serotonin was approximately 17 times more effective under these conditions in promoting uterine water imbibition than was histamine.

In the case of serotonin, as in the case of histamine and of intraluminal estrogen, uterine hyperemia was clearly evident 4 hr after application. The time of onset of vasodilatation in the response to these substances was virtually instantaneous when they were applied under direct observation to the mesometrial surface in the form of a fine stream.

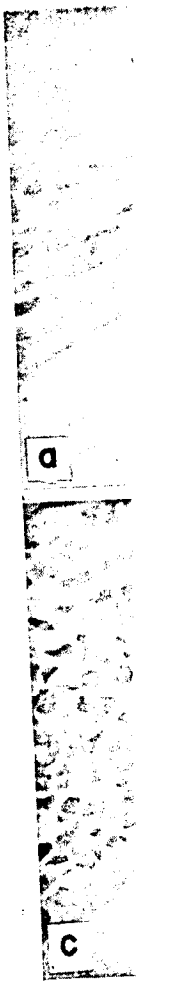
In addition to their effects on adult, ovariectomized rats, both histamine (1 mg I.L.) and serotonin (0.25 mg I.L.) were capable of eliciting full-blown uterine water and hyperemia responses in 21-day-old intact Sprague-Dawley animals.

These data gain specificity from the failure of heparin treatment (Group VIII) to produce an alteration of the uterine water levels from control values. Nor was there noted any hyperemic response to the topical administration of heparin.

LATER EFFECTS OF HISTAMINE, SEROTONIN AND HEPARIN

It is of critical importance to analysis of the mechanism of action of the naturally-occurring substances demonstrated to be estrogenicomimetic to determine whether these materials resemble the later, as well as the acute actions of the hormone. Thus, are evocation of hyperemia and increased capillary permeability adequate to stimulate the metabolic events required for support of true growth of the target tissue in terms of ultimate changes in structure and composition? Preliminary experiments[3] had indicated (Spaziani and Szego, 1957) that intrauterine histamine application in the ovariectomized rat was associated 24 hr

[3] The authors are indebted to Dr. John G. Pierce and Dr. John D. Green for helpful advice in connection with these experiments.



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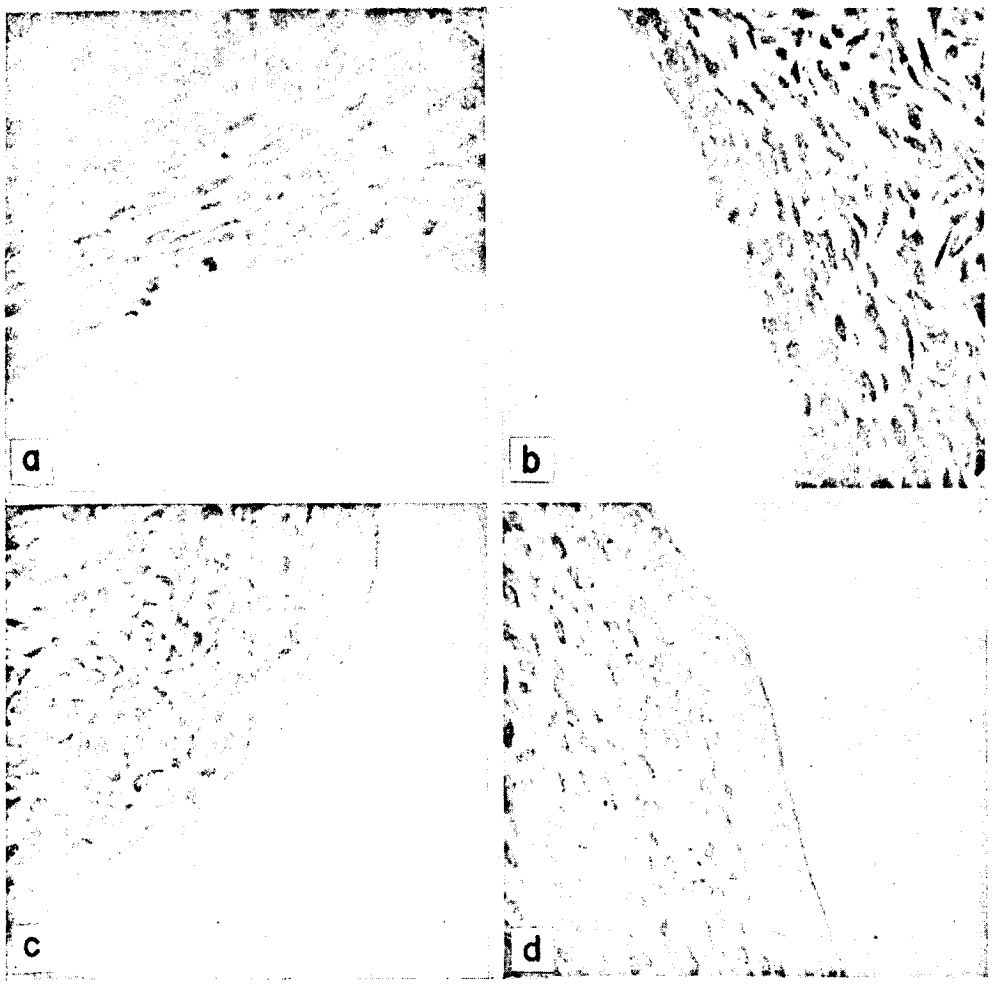

FIG. 1. Histologic appearance of uterine sections of ovariectomized rats receiving intraluminal injections 24 hr earlier. Fixation in neutralized formalin; hematoxylin-eosin stain (×440). a. Estradiol-17β in the equivalent of 1.8% saline, 0.1 μg/0.02 ml/horn. Note prominent mitotic figures in luminal epithelium. b. Histamine, 1 mg/horn. c. Serotonin, 0.25 mg/horn. d. Heparin, 3 mg/horn. Note occurrence of mitotic activity in b and c but not in d.

later with the occurrence of substantial numbers of mitoses in the luminal epithelium and an increase in glandular activity. These findings, which have recently been extended by Spaziani (1961), are confirmed in the present study (Fig. 1b). Serotonin is relatively less effective in evoking evidences of later uterine growth notwithstanding its activity in stimulating the initial vasomotor effects and fluid shifts in the target tissue (Fig. 1c). Intraluminal estrogen treatment invariably stimulated mitotic activity under these conditions (Fig. 1a). Heparin had no clearly discernible effect (Fig. 1d) when compared with appropriate controls (Fig. 2).

EFFECTS OF SEROTONIN ANTAGONISTS

A limited number of studies has been carried out on the capacity of serotonin inhibitors (Fig. 3) to modify the effectiveness of estrogen on early uterine growth. These studies are summarized in Tables 4 and 5.

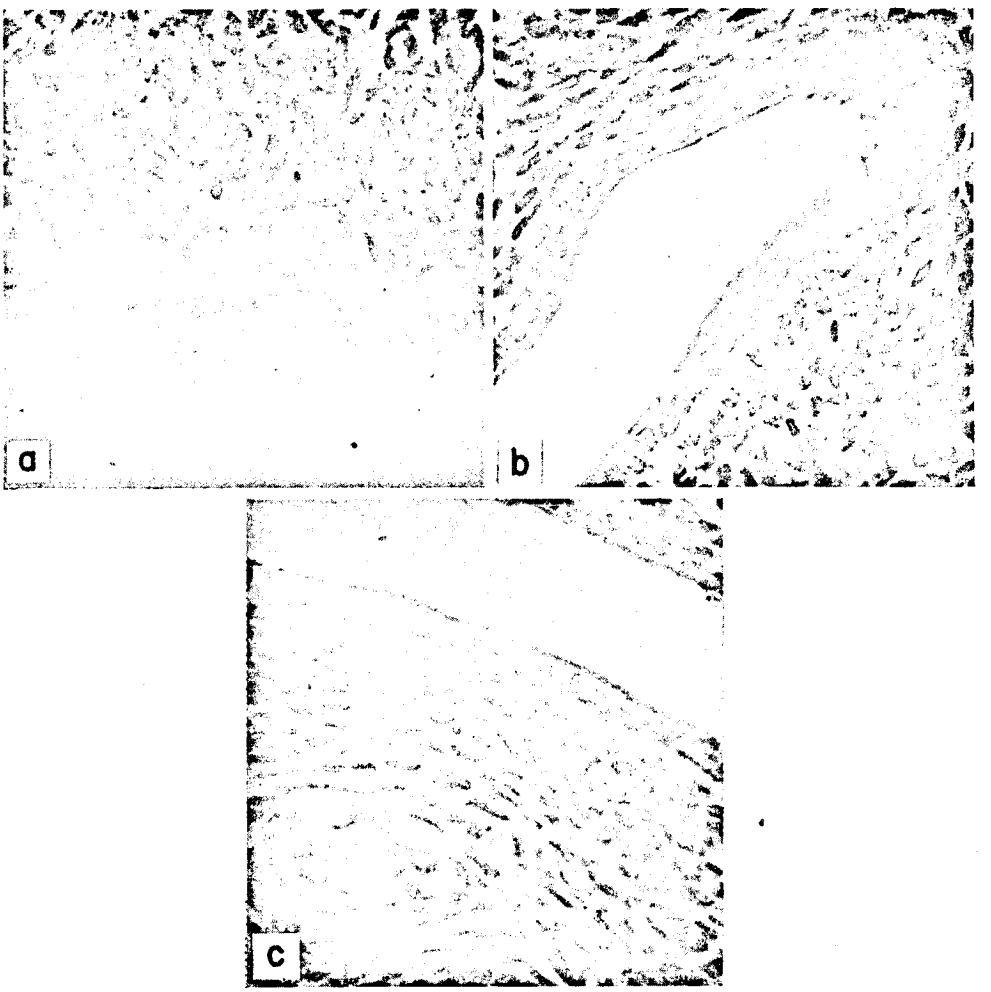

FIG. 2. Histologic appearance of uterine sections of control ovariectomized rats. Fixation in neutralized formalin; hematoxylin-eosin stain (×440). a. Untreated castrate. b. Animal sacrificed 24 hr after intraluminal injection of 0.02 ml/horn of 1.8% saline. c. Similar animal receiving 3.36% saline. Note absence of mitotic activity in luminal epithelium.

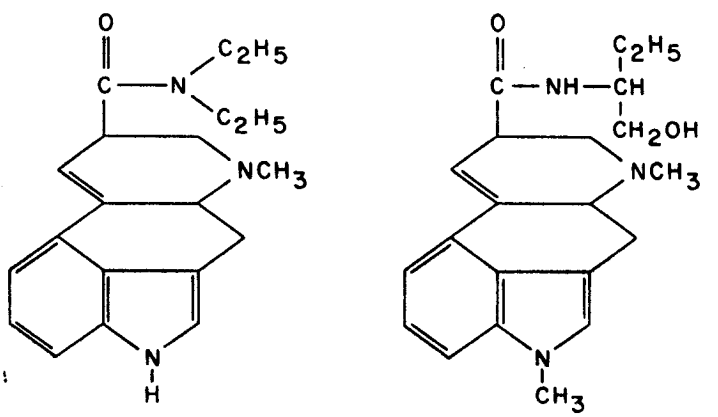

FIG. 3. Structural formulas of serotonin inhibitors used to obtain data in Tables 4 and 5

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TABLE 4

INFLUENCE OF INTRAVENOUSLY ADMINISTERED LSD-25 AND UML-491 ON THE UTERINE WATER IMBIBITION RESPONSE TO ESTRADIOL-17β[a]

Group	Description	Number animals	% H_2O[b]	"P"	Compared with group number
I	Estradiol-17β, 0.5μg/100 gm B.W., I.V.	9	85.2 ± 0.19		
II	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 1 mg LSD-25, I.V.	9	81.2 ± 0.47	<0.001	I
III	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 1 mg LSD-25, I.V.; adrx.	8	83.4 ± 0.50	0.01 0.01	II I
IV	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 2 mg LSD-25, I.V.	4	81.3 ± 0.63	<0.001	I
V	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 2 mg LSD-25, I.V.; adrx.	3	84.4	—	—
VI	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 4 mg LSD-25, I.V.	5	79.4 ± 0.74	<0.001 0.1	I II
VII	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 4 mg LSD-25, I.V.; adrx.	4	84.4 ± 0.30	<0.001 0.3	VI I
VIII	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 5 mg UML-491, I.V.	3	84.5	—	—

[a] Where adrenalectomy is indicated, surgery was performed immediately prior to injections. As indicated in the text, inhibitor was injected first, followed by estradiol. Routes of injection as indicated.

[b] Deviations shown are S.E.M.

It may be noted (Table 4) that LSD-25, given I.V. in a fixed dose of 1, 2, or 4 mg per animal, produced a striking depression of the response to estrogen ($p < 0.001$). This inhibition was relieved by adrenalectomy just prior to injection. Relief of the LSD-25 blockade by adrenalectomy had been anticipated after the first experiment with this compound because of the profoundly stressful effects of the drug. As has been demonstrated from these laboratories, adrenocortical hyperactivity induced by stress or ACTH inhibits uterine sensitivity to estrogen. Adrenalectomy overcomes this effect (Szego and Roberts, 1948, 1953). It also became apparent that the rats receiving LSD-25 suffered a decline in body temperature (Rothlin, 1957). An external source of heat was provided by infrared heating of the cage area. The rectal temperatures of animals so maintained were between 37.5 and 39°C at autopsy.

The likelihood that the depressive effect of I.V. LSD-25 was attributable to generalized stress rather than to specific blockade of a possible serotonin trigger for estrogen action is also supported by the failure of I.V. UML-491[2] at five times the maximally effective LSD-25 dose to evoke any change in estrogen sensitivity (Table 4). UML-491, a powerful anti-serotonin (Doepfner and Cerletti, 1958) did not evoke the behavioral effects seen with LSD.

Table 5 depicts the results of similar experiments in which LSD was administered

TABLE 5

INFLUENCE OF INTRALUMINALLY ADMINISTERED LSD-25 AND UML-491 ON THE UTERINE WATER IMBIBITION RESPONSE TO ESTRADIOL-17β[a]

Group	Description	Number animals	% H_2O[b]	"P"	Compared with group number
I	0.9% saline I.V.[c]; LSD-25, 0.25 mg	3	80.4	—	—
II	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; 1.8% saline I.L.	8	83.6 ± 0.23	—	—
III	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; LSD-25, 0.25 mg I.L.	8	83.4 ± 0.32	0.7	II
IV	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; LSD-25, 0.4 mg[d] I.L.	4	82.4 ± 0.10	>0.01, <0.02	III
V	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; LSD-25, 2 mg[d] I.L.	8	82.3 ± 0.40	>0.01, <0.02	II
VI	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; LSD-25, 2 mg[d] I.L.; adrx.	6	82.1 ± 0.40	0.8	V
VII	Estradiol-17β, 0.5μg/100 gm B.W., I.V.; UML-491, 0.1 mg[d] I.L.	4	84.5 ± 0.13	<0.01	II

[a] Where adrenalectomy is indicated, surgery was performed immediately prior to injections. As indicated in text, inhibitor was injected first, followed by estradiol or control saline. Volumes of all I.L. injections constant at 0.02 ml/each horn. Dosages are indicated per horn.

[b] Deviations shown are S.E.M.

[c] Volume of I.V. saline was equivalent to that of estradiol in groups following (0.5 ml/100 g B.W.).

[d] Final osmolarity ≅ 1.8% saline.

intraluminally. By this route doses ranging from 0.4 mg to 2 mg/horn were effective in antagonizing estrogen. It will be noted that the intraluminal administration of 2 mg clearly depressed the uterine water level as compared to the controls (Group V versus II). However, the responses of the adrenalectomized animals receiving this dosage were *also* depressed to the equivalent degree (Group V versus VI; $p = 0.8$). Thus, adrenalectomy does not appear to protect estrogen sensitivity from LSD depression when the intraluminal route is used. It will be noted from Table 5 (Group VII) that UML-491 at 0.1 mg/horn (the upper limit of dosage for reasons of solubility), did not depress the estrogen-induced uterine water imbibition.

DISCUSSION

Previous work from these laboratories has implicated estrogen-induced liberation of intrinsic histamine in mediation of acute hormonal stimulation of the target. The decline in endogenous uterine histamine following estrogen administration to the castrate rat has received independent confirmation (Shelesnyak, 1959). Histamine, serotonin, and heparin coexist in the mast cell which undergoes degranulation under the influence of estrogen. Because of the likelihood of simultaneous discharge, from this or other sites of localization, of more than one of these substances on administration of certain so-called "histamine releasers" to the rat (Bhattacharya and Lewis, 1956; Halpern *et al.*, 1957), it became important to extend the earlier investigations to the examination of the possible capacity of serotonin and of heparin to simulate estrogen action.

The present experiments reveal that serotonin is capable of reproducing some characteristic uterine effects of estrogen in

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the ovariectomized rat, as was previously demonstrated with histamine. Heparin, on the other hand, was inert. Regardless of its capacity to induce both early and later uterine responses akin to those elicited by estrogen and by histamine, the question arises whether serotonin participates in estrogen action.

It might be concluded from the experiments in which inhibitors were administered *intravenously* (Table 4) that serotonin is not a likely concomitant of estrogen action because the data revealed that adrenocortical hyperactivity was responsible for the inhibition seen with LSD under these conditions.

It may be recalled that the antihistamines capable of blocking estrogen action in the earlier study were administered intraluminally in order to permit adequate local concentrations (Spaziani and Szego, 1959). When similar experiments were conducted in the present series with intraluminally administered LSD-25, adrenalectomy did *not* protect against the depressing action of this drug on estrogen sensitivity (Table 5). In contrast to the local effectiveness of LSD-25, which is a highly specific serotonin antagonist (Gaddum and Hameed, 1954), the closely related compound, UML-491, did not block the acute actions of estrogen at 0.1 mg/horn I.L. (Table 5). Because of solubility limitations this observation could not be extended. As yet, no comprehensive survey has been made of additional serotonin inhibitors, some of which might function under these conditions.

No simple explanation of LSD-serotonin interaction is sufficient to account for the antagonism of serotonin by LSD at some receptors, but not at other sites (Vogt, 1958). Nor does it necessarily follow from the demonstrated anti-serotonin activity of UML-491 with respect to edema of the rat paw (Doepfner and Cerletti, 1958) that this compound would antagonize the vasodilator properties of the amine in the uterus. Thus, these considerations do not rule out the participation of serotonin, in addition to histamine, in early estrogen-induced uterine growth.

It is conceivable, however, that if serotonin is demonstrated to play a physiologic role it may be one of support, in view of the fact that serotonin itself is capable of inducing histamine release (Feldberg and Smith, 1953; Page and McCubbin, 1956), thus augmenting the action of estrogen in this regard. Such a possibility is under investigation, and gains some support from the relatively smaller effect of serotonin than of histamine on later evidences of uterine stimulation associated with true growth.

The limited number of controlled studies in the literature on the stimulatory influence of locally instilled histamine on morphologic aspects of uterine growth has been cited in detail elsewhere (Spaziani and Szego, 1959). The present investigations, confirming and extending earlier observations from these and other laboratories (Spaziani and Szego, 1957; Spaziani, 1961), also reveal that histamine can indeed stimulate epithelial mitotic activity in the uterus 24 hr after instillation. Moreover, serotonin was also effective by this criterion, but to a more limited degree than was histamine. Although a five-fold dose difference in estradiol-17 β (0.02 μg/horn versus 0.1 μg/horn) could be distinguished clearly by differences in numbers of mitoses per section, it was apparent that such histologic criteria are too gross for more than semi-quantitative correlation. Indeed, the control tissues themselves, notwithstanding their generally atrophic character, showed a rare mitotic figure in the surface epithelium. Nevertheless, in keeping with the capacity of histamine and serotonin to induce the acute hyperemia and edema which distinguish early uterine growth, the 24-hr sequelae of treatment with these substances include stimulation of mitotic activity characteristic of the true growth phase of estrogen action. It cannot be determined whether simple inflammation due to nonspecific irritants would lead to similar effects, since their presence is accompanied by local histamine and possibly serotonin release. Moreover, the possibility is not excluded by the present study that bradykinin or a related peptide, having

vasodilator and capillary permeability-increasing properties (cf. Croxatto and Barnafi, 1960), and released from specialized loci by many "histamine-releasers" (Gaddum, 1959), may function along lines similar to those described for histamine and serotonin in these and earlier investigations. Thus, no firm conclusions can be drawn from the above data regarding the closeness of association between stimulation of the primary and of the secondary growth phases of the uterine response by histamine and serotonin. Indeed, some degree of dissociation has already been indicated between the early hemodynamic-fluid redistribution effect and later structural modifications of the target tissue (Szego and Roberts, 1953; Goodman *et al.*, 1957). Apparently complete blockade by cortisol of the acute inflammatory response of the uterus to estrogen characterized by hyperemia and water imbibition did not prevent some degree of hypertrophy and hyperplasia 20 hr after steroid treatment (Szego and Roberts, 1953).

From work in progress it remains to be seen whether the effects of histamine and serotonin on metabolic processes other than those herein studied are also similar in direction to the influence of estrogen on the uterus.

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