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Effect of Histamine Receptor Agonists and Antagonists on the Uterine Vasculature[1] (41823)

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Abstract. Histamine H_1 and H_2 receptors are known to exist in uterine smooth muscle; however, neither receptor has been clearly identified in the uterine vasculature. In the present study, 12 nonpregnant ewes were chronically instrumented with catheters in the carotid artery, jugular vein, uterine arteries, and electromagnetic flow probes on the uterine arteries for continuous measurement of uterine blood flow. Dose response curves were determined for bolus injections of Histamine (1–10 μg), the H_1 receptor agonist 2PEA (10–100 μg), and the H_2 receptor agonist Dimaprit (30–300 μg) before H_1 receptor blockade with pyrilamine, following H_1 receptor blockade, and following H_2 receptor blockade with metiamide. Uterine vasodilator responses to histamine and 2PEA were essentially abolished by pyrilamine, while responses to dimaprit were not altered. Following addition of metiamide, responses to histamine were reduced further and responses to dimaprit were abolished. Baseline uterine blood flow was not altered by either H_1 or H_2 receptor blockade or their combination. Intraarterial bolus injections of the mast cell histamine-releasing compound 48/80 (100–1000 μg) had no effect on uterine blood flow. These experiments demonstrate that the uterine vasculature of the ovine contains almost exclusively H_1 receptors, does not contain compound 48/80 sensitive mast cells and is not dependent upon endogenous histamine to maintain blood flow.

The role of histamine in regulating hemodynamics has been extensively investigated in both the systemic and peripheral circulation (1). This biogenic amine is known to act by stimulation of two distinct receptors which have been identified as H_1 and H_2 (2, 3). Specific agonists and antagonists currently exist for both H_1 and H_2 receptors. These pharmacological agents have allowed the determination of the precise role of histamine in a number of physiological events.

The physiological role of histamine in the uterus has been the subject of numerous publications. Histamine has been implicated in implantation (4), uterine tissue growth (5), and estrogen-induced increases in uterine blood flow and edema (6, 7). In addition, histamine H_2 receptors have been shown to produce relaxation of the rat uterus (3, 8). Investigation into the uterine vascular effects of histamine have been limited. Holden (9) first showed that topical administration of histamine lead to vasodilation of the uterine vasculature in the rat, and Spaziani and Szego reported similar results following uterine intraluminal administration of histamine (6). Recently Harvey and Owen (10) have demonstrated that systemically administered histamine, the H_1 receptor agonist 2PEA, and the H_2 receptor agonist 4-methyl histamine can produce uterine vasodilation in rats. In their study, the histamine-induced vasodilation was not altered by either mepyramine or metiamide alone, but could be blocked with the combination of H_1 and H_2 receptor antagonists. Specific blockade of H_1 and H_2 receptor agonists, however, was not evaluated. Resnik and co-workers (11) have shown that histamine-induced vasodilation in the ovine uterine vasculature can be significantly attenuated by the H_1 receptor antagonist diphenhydramine, but their investigation made no attempt to evaluate the effects of either H_2 receptor agonists or antagonists.

The present study was designed to determine if H_1 and H_2 histamine receptors exist in the uterine vasculature of the nonpregnant ovine, and if endogenously occurring histamine plays an important role in maintaining uterine blood flow. In addition, the existence

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of mast cell histamine in the ovine uterine vasculature was assessed by use of the mast cell histamine-releasing compound 48/80.

Methods. *Surgical preparation.* Twelve nonpregnant ewes of mixed breed, were chronically instrumented as previously reported (12). Briefly, nonpregnant ewes weighing 35 to 65 kg were sedated with valium (10 mg im) and placed in the left lateral recumbent position. Following infiltration with xylocaine (2% solution), the carotid artery and jugular vein were dissected free and cannulated with polyvinyl catheters threaded proximally to the level of the aortic root and superior vena cava, respectively. Catheters were placed in a cloth pouch attached to the ewe's neck.

Animals were further sedated with sodium thiopental (250 mg), received a hyperbaric spinal (pontocaine HCl, 12 mg), and were then placed in the supine position. The uterus was exposed by a 15–20 cm midline abdominal incision and the right and left main uterine arteries were fitted with electromagnetic flow probes of appropriate size. A lateral branch of each uterine artery was catheterized with a polyvinyl catheter. This catheter was placed distally to the flow probe and allowed direct intraarterial administration of compounds. All animals were bilaterally ovariectomized to prevent fluctuations in uterine blood flow which occur in the estrus cycle. Catheters and flow probe cables were passed subcutaneously to the left side of the sheep and placed in a cloth pouch secured to the ewe's side. All catheters were filled with heparin (1000 units/cc) to maintain patency.

Following surgery, animals were placed in portable cages and received water and commercial feed *ad libitum.* Ewes were allowed to recover from surgery for a period of 5 days prior to testing and were kept in the laboratory for the duration of the experiments. Each ewe received an intravenous injection of estradiol-17β (1 μg/kg) every evening (4–5 PM) to prevent uterine atrophy which would occur because of castration.

Uterine arterial blood flow (UBF) was monitored with a square-wave electromagnetic flow meter (Dienco RF-1000, Los Angeles, Calif.). Electromagnetic flow probes were calibrated with saline prior to implantation and were found to be linear over a range of 0–300 ml/min. Flow meters were equipped with electronic zeroes which were verified as being accurate during vascular occlusion. Mean systemic arterial pressure (MAP) was monitored by strain gauge pressure transducers (MP-4, Micron Instrument Company, Los Angeles, Calif.); heart rate (HR) was determined by a cardiotachometer (Beckman Instrument Co., Fullerton, Calif.). All parameters were continuously recorded using a pen writing recorder (Beckman Dynograph R-612, Beckman Instrument Co., Fullerton, Calif.).

All systemic responses were recorded as percent change from baseline levels, while uterine vasodilator responses were calculated as an absolute change in uterine blood flow. Statistical comparisons were made using the student's paired t test as described by Steel and Torrie (24); the level of significance was $P < 0.05$.

Bolus injections of H_1 and H_2 receptor agonist. On the day of testing, doses of histamine, H_1 receptor agonist 2PEA 2 (2-pyridyl) ethylamine, and H_2 receptor agonist (dimaprit) were given as bolus injections into the uterine artery. Doses of each drug were given in a completely random order. Dose response curves for each drug were constructed before H_1 receptor blockade, after H_1 receptor blockade and after combined H_1 and H_2 receptor blockade. Spot checks with the appropriate agonist confirmed effectiveness of the blockade throughout the experiments. All monitored parameters were allowed to return to preinjection levels before the next dose was tested.

H_1 receptor blockade was achieved by administration of pyrilamine (2.5 mg/kg) into the jugular vein, while H_2 receptors were blocked by the antagonist metiamide (1 mg/kg). A second dose of pyrilamine (2.5 mg/kg) was administered at the same time as metiamide to assure that both H_1 an H_2 histamine receptors were blocked during the third test period. In a second group of animals, the order of blockade was reversed and responses to histamine were determined prior to H_1 and H_2 receptor blockade, after H_2 receptor blockade (metiamide 1 mg/kg), and again after the addition of H_1 receptor blockade (pyrilamine 2.5 mg/kg).

Ten-minute continuous infusion of histamine, 2PEA, and dimaprit. Several reports have appeared (13–15) suggesting that differing amounts of time are required to stimulate H_1

and H_2 histamine receptors. In these studies, responses to the H_1 receptor agonist occurred quickly and the response decreased with time; in contrast responses to H_2 receptor agonist increased slowly with responses peaking several minutes after the infusion was begun. To test if this occurred in the ovine uterine vasculature, 10-min infusions of histamine (1 μg/min), 2PEA (30 μg/min), and dimaprit (300 μg/min) were undertaken in five animals.

Bolus injections of the mast cell histamine releasing compound 48/80. Experiments were conducted to determine if endogenously occurring histamine was stored in compound 48/80 sensitive mast cells in the ovine uterine vasculature. The mast cell histamine releasing compound 48/80 was administered as intraarterial boluses of 100, 300, or 1000 μg and the responses were recorded. Doses were given in a random order.

Drugs used. Solutions of histamine dihydrochloride, compound 48/80, pyrilamine maleate (Sigma Chemical Co., St. Louis, Mo.), 2-(2-pyridyl)-ethylamine (2PEA), and dimaprit (Smith, Kline and French Lab, Ltd.) were prepared in saline. Metiamide (Smith, Kline and French Lab, Ltd.) was dissolved in 1 *N* HCl, neutralized with NaOH, and the final solution was diluted in saline. Solutions for intraarterial bolus injections of the agonist were prepared in concentrations of 1, 10, 100, and 1000 μg/ml and were injected in volumes of either 0.3 or 1.0 ml. For the intraarterial infusion study agonist solutions were administered at the rate of 0.1 ml/min. All doses are expressed as the free base.

Results. *Uterine blood flow responses to bolus injections of histamine, 2PEA, and dimaprit in the nonpregnant ewe.* Dose–response curves for histamine, 2PEA, and dimaprit were created by intraarterial bolus injection of each compound directly into the uterine artery (N = 5 for each agonist). In these animals baseline values for uterine blood flow were 7 ± 1 ml/min ($\bar{X}$ ± SEM) and increased in a dose-related fashion as is shown in Fig. 1. On an equal weight basis, histamine was approximately ten times more potent as a uterine vasodilator than 2PEA and at least a thousand times more potent than the H_2 receptor agonist, dimaprit. At the doses used, the effects of these vasoactive compounds were limited to the uterine vasculature, except at the highest doses of histamine and 2PEA which produced a significant increase in heart rate. None of the agents altered systemic arterial pressure at the doses tested.

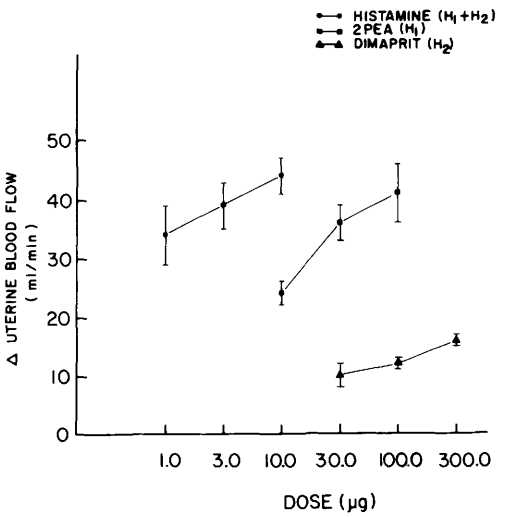

FIG. 1. Effect of local intraarterial bolus injections of histamine, 2PEA, and dimaprit on uterine blood flow versus dose. Values represent absolute changes in milliliters per minute from baseline and represent the mean ± SEM for five animals.

Uterine blood flow responses to 10-min infusions of histamine, 2PEA, and dimaprit. Ten-minute infusions of histamine (1 μg/min), 2PEA (30 μg/min), and dimaprit (300 μg/min) were evaluated to determine if H_2 receptors required longer periods of stimulation to produce maximal vascular responses compared to H_1 receptor agonists, as has been reported in other vascular beds (13–15). The pattern of the vascular response to 10-min infusions of each agonist is depicted in Fig. 2. All three compounds, histamine, 2PEA, and dimaprit showed similar time-response patterns. Baseline uterine blood flow averaged 12 ± 3 ml ($\bar{X}$ ± SEM) prior to intraarterial infusion of the H_1 and H_2 receptor agonist.

Effect of H_1 and H_2 receptor blockade on vascular responses to bolus injections of histamine. The dose-related responses of the uterine vasculature to bolus injections of histamine were virtually abolished following administration of the H_1 histamine receptor blocking agent pyrilamine (Fig. 3). Subsequent administration of the H_2 receptor blocker,

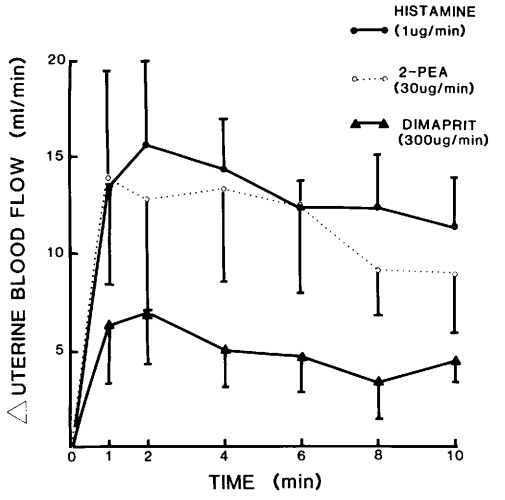

FIG. 2. Effect of 10-min continuous infusions of histamine, 2PEA, and dimaprit on uterine blood flow. Values represent the absolute change in milliliters per minute from baseline (baseline blood flow was 12 ± 3 ml/min, $\bar{X}$ ± SEM) and represent the mean ± SEM for five animals. All three agents responded with identical time courses.

metiamide, led to a further but nonsignificant reduction in vasodilator responses to histamine. When the order of blockade was reversed in a second group of animals ($N = 2$), responses to histamine were not altered after administration of the H_2 receptor antagonist metiamide, but were abolished with the addition of pyrilamine. The tachycardia observed with the highest dose of histamine (see above) was abolished by pretreatment with pyrilamine. These data suggest that the ovine uterine vasculature contains mainly H_1 histamine receptors.

Effects of H_1 and H_2 receptor blockade on the uterine vascular responses to bolus injections of the H_1 receptor agonist, 2PEA. The effects of the H_1 receptor agonist 2PEA on uterine blood flow are illustrated in Fig. 4. 2PEA, like histamine, produced a dose-related increase in uterine blood flow. Pretreatment with the H_1 receptor blocking agent pyrilamine essentially abolished the uterine vascular responses to 2PEA. Subsequent administration of the H_2 antagonist, metiamide, did not lead to any additional reduction in 2PEA uterine responses. When the order of blockade was reversed in a second group of animals ($N = 2$), uterine responses to 2PEA were not altered by metiamide pretreatment, but were abolished by pyrilamine. The tachycardia observed

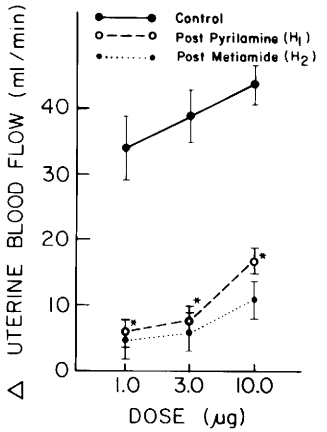

FIG. 3. Effect of local intraarterial injections of histamine before (control), after H_1 receptor blockade with pyrilamine (post pyrilamine) and after addition of H_2 receptor blockade with metiamide (postmetiamide) on uterine blood flow versus dose. All values are absolute changes in milliliters per minute from preinjection baseline and represent the mean ± SEM for five animals. Asterisks indicate responses to histamine obtained after pyrilamine were significantly less than control ($P < 0.05$). Further reduction in responses after metiamide were not significantly different from postpyrilamine values.

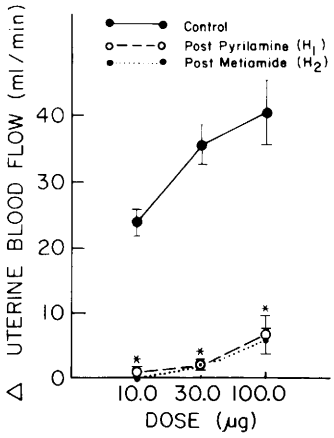

FIG. 4. Effect of local injections of 2PEA (2-(2-pyridyl) ethylamine) before (control), after H_1 receptor blockade with pyrilamine (postpyrilamine) and after addition of H_2 receptor blockade with metiamide (postmetiamide) on uterine blood flow verus dose. All values are absolute changes in uterine blood flow (ml/min) from preinjection baseline and represent the mean ± SEM for five animals. Asterisks indicate responses to 2PEA obtained after pyrilamine were significantly less than control ($P < 0.05$). 2PEA responses were not altered further after the addition of H_2 receptor blockade with metiamide.

at the highest dose of 2PEA tested was abolished by pretreatment with pyrilamine.

Effects of H_1 and H_2 receptor blockade on the uterine vascular response to bolus injections of the H_2 receptor agonist, dimaprit. The results of intraarterial injections of the H_2 receptor agonist, dimaprit, are shown in Fig. 5. Dimaprit is a weak dilator of the uterine vasculature in the nonpregnant ewe. Responses to dimaprit were not significantly altered after pretreatment with pyrilamine but were abolished following pretreatment with the H_2 receptor antagonist, metiamide. At the doses tested, dimaprit did not significantly alter systemic arterial pressure or heart rate. When the order of blockade was reversed in a second group of animals (N = 2), responses to dimaprit were nearly abolished after metiamide, and addition of pyrilamine did not result in further alteration of the uterine response to dimaprit. These data suggest that a limited number of H_2 receptors do exist in the ovine uterine vasculature.

Role of histamine in maintaining uterine blood flow in the nonpregnant ovine. During the intravenous administration of pyrilamine, uterine blood flow decreased from baseline values, but returned to control levels within 5 min. Subsequent administration of metiamide did not result in further alteration in uterine blood flow. The observation that the combined blockade of H_1 and H_2 histamine receptors (verified by specific agonist) did not significantly alter baseline uterine blood flow suggests that under the present experimental conditions histamine is not important in maintaining uterine blood flow in the nonpregnant animal.

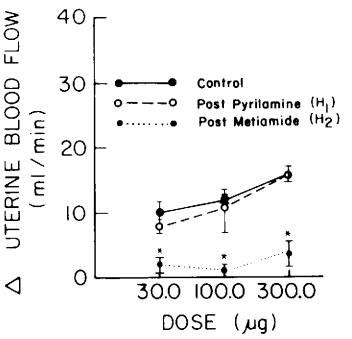

FIG. 5. Effect of local injections of dimaprit before (control), after H_1 receptor blockade with pyrilamine (postpyrilamine) and after addition of H_2 receptor blockade with metiamide (postmetiamide) on uterine blood flow versus dose. All values are absolute changes in uterine blood flow (ml/min) from preinjection baseline and represent the mean ± SEM for five animals. The asterisks indicate responses to dimaprit obtained after the combination of pyrilamine and metiamide were significantly ($P < 0.05$) less than those obtained during control or postpyrilamine periods.

Effect of the mast cell histamine releasing compound 48/80 on uterine blood flow. Injection of the mast cell histamine releasing compound 48/80 (16) in doses ranging from 100 to 1000 μg did not significantly affect uterine blood flow in the four animals tested. In addition, no systemic (arterial blood pressure or heart rate) effects were observed.

Discussion. The importance of histamine in the uterine vasculature has been the subject of a number of scientific reports over the past 60 years. This biogenic amine has been implicated in several physiologic phenomena which occur in the uterus including estrogen-induced increases in uterine blood flow (6, 7, 9, 17), uterine edema (17) and implantation (4, 18). The majority of this work has dealt with rodents, where direct observation of the vascular action of compounds can occur in only one of three ways. First, the compound can be applied topically to the uterine parametrial blood vessels as was done originally by Holden (9). This method does not allow quantitation of vascular concentrations, and alterations in vascular diameter may result from contractions of nonvascular tissue. Second, the local uterine vascular effects can be observed either directly or by administration of radiolabeled microspheres (10) after the compound is administered systemically. This methodology results in a mixture of uterine and systemic effects which may be difficult to separate. Third, the agent can be directly applied into the uterine lumen. This method has been used by Spaziani and Szego (6), but may lead to severe uterine damage (19), thus erroneous data.

The present experiments have used the unanesthetized chronically instrumented nonpregnant ewe to investigate the effects of histamine and its specific H_1 and H_2 receptor agonists on the uterine vasculature. In this preparation, histamine or its specific H_1 and H_2 receptor agonists (2PEA and Dimaprit, respectively) were injected directly into the uterine vasculature. Following quantitation of

vascular responses to histamine and specific H_1 and H_2 receptor agonists, histamine receptor antagonists were used to selectively block these responses.

Histamine produced a dose-related increase in uterine blood flow and was found to be a more potent vasodilator (on an equal weight basis) than the other H_1 and H_2 receptor agonists tested (Fig. 1). The uterine vascular responses to histamine were significantly attenuated (Fig. 3) while responses to the specific H_1 receptor agonist, 2PEA (20), were nearly ablated after pretreatment with H_1 antagonist, pyrilamine (Fig. 4). The disappearance of 2PEA responses demonstrates that the dose of pyrilamine used is adequate to block H_1 receptors. These data suggest that the uterine vasculature of the ovine contains mainly H_1 receptors.

The existence of H_2 receptors is suggested by the additional reduction of the vascular responses to histamine following pretreatment with the H_2 receptor antagonist, metiamide (Fig. 3). Further evidence that H_2 receptors exist in the uterine vasculature of the nonpregnant ewe is provided by the response to the H_2 agonist, dimaprit. Dimaprit is a specific H_2 receptor agonist (21) and Fig. 4 shows that dimaprit can produce small but dose-related increases in uterine blood flow which are not altered by the H_1 receptor antagonist, pyrilamine, but are totally ablated by the H_2 receptor antagonist, metiamide. Failure of pyrilamine to alter responses to dimaprit suggests that at least in the ovine uterus, pyrilamine acts as a specific H_1 receptor antagonist.

In the present study, similar results were seen when the order of the H_1 and H_2 receptor blocking agents was reversed. Responses to histamine and 2PEA were not modified following metiamide, but uterine responses to dimaprit were abolished. Following the addition of pyrilamine, responses to histamine and 2PEA were ablated. The failure of metiamide alone to alter uterine responses to histamine is similar to what has been observed in other vascular beds (22).

The lack of identification of large numbers of H_2 receptors in the ovine uterine vasculature in the present study does not appear to be due to inadequate exposure of the H_2 histamine receptors to the H_2 receptor agonist as has been reported in other vascular beds (13–15). This observation is based on the fact that infusion of the H_2 receptor agonist, dimaprit, produced a time-response pattern which was virtually identical to that observed with both histamine and the H_1 receptor stimulant, 2PEA.

These data demonstrate that both H_1 and H_2 receptors exist in the ovine uterine vasculature. However, the physiological significance of the small number of H_2 receptors is presently unknown, and the observation may be only of pharmacological interest. It does seem possible, however, that the number of H_1 and H_2 receptors could change during both the estrus cycle and pregnancy.

The observation that uterine vasodilation after intraarterial injections of histamine is mediated by mainly H_1 receptors confirms the work of Resnik *et al.* (11) which showed that responses to histamine in sheep were significantly reduced following administration of diphenhydramine, an H_1 receptor antagonist. These workers investigated the possible role of histamine in mediating estrogen-induced increases in uterine blood flow but did not evaluate the effects of specific H_1 and H_2 receptor agonists on the uterine vasculature. In a second study in sheep, Woods *et al.* (23) investigated the effects of intraaortically administered histamine on common internal iliac blood flow (only 10–20% of this blood flow goes to the uterus of the nonpregnant ewe). They found that diphenhydramine only partially attenuated common internal iliac responses to histamine, and that metiamide did not alter vascular responses at all. These results are difficult to interpret since the responses observed are a mixture of responses from several vascular beds (uterus, bladder, cervix, vagina, as well as some muscles in the back) and the combinations of the H_1 and H_2 receptor antagonists were not evaluated.

The present study suggests that histamine does not play a major role in maintaining uterine blood flow in the nonpregnant ovine, since baseline uterine blood flow was not altered by either pyrilamine, metiamide, or the combination of the antagonists at doses which totally blocked H_1 and H_2 receptors. In addition, attempts to release endogenous histamine from mast cells in the uterine vasculature of the nonpregnant ewe were unsuccessful. Doses of compound 48/80 as high as 1 mg administered directly into the uterine artery were without any vascular response.

However, because of the experimental protocol it is possible that daily estrogen treatment may have depleted mast cell histamine stores (8) or that uterine artery mast cells may require sustained exposure to compound 48/80 which would not occur following a bolus injection. Furthermore, this study does not rule out the possibility that the uterine arteries might contain non-mast cell histamine which could result in vasodilation of the uterine vasculature.

In summary, the uterine vasculature of the nonpregnant ovine appears to contain both H_1 and H_2 receptors. Responses to histamine appears to be mainly due to stimulation of histamine H_1 receptors. Endogenous histamine does not appear to play a major role in maintaining uterine blood flow, since blood flow did not change after H_1 and H_2 receptor blockade. The present study also suggest that compound 48/80 sensitive mast cells are not present in the ovine uterine vasculature. This study, however, does not rule out the possible hemodynamic role of non-mast cell histamine nor has it investigated the possibility that H_1 and H_2 receptor populations may change during the estrus cycle or during pregnancy.

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