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Inhibitory Action of Alpha-Melanocyte Stimulating Hormone on Lordosis in Rats: Possible Involvement of Serotonin[1,2]

LYN H. RAIBLE

Department of Psychology, Kalamazoo College, Kalamazoo, MI 49007

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RAIBLE, L. H. *Inhibitory action of alpha-melanocyte stimulating hormone on lordosis in rats: Possible involvement of serotonin.* PHARMACOL BIOCHEM BEHAV **30**(1) 37–43, 1988.—Alpha-melanocyte stimulating hormone (MSH) has been found to exert a short- and a long-term inhibitory action on lordosis. The present series of experiments examined the possibility that these effects are mediated by MSH-induced alterations in activity at serotonin type II receptors. In Experiment 1, quipazine (serotonin type II agonist) was found to significantly attenuate the short-term effect of MSH while only partially attenuating the long-term action of MSH. In the second experiment, doses of MSH and of pirenperone (serotonin type II antagonist) that did not inhibit lordotic responding when administered alone were found to inhibit responding when administered together. It was also found that 20 ng MSH produced a long-term, but not a short-term inhibition of receptivity. The results of Experiment 3 indicated that the inhibition observed in Experiment 2 could be reversed by quipazine. These results suggest that alterations in serotonin activity are one mechanism by which the effects of MSH are produced. The relevance of this to the regulation of reproductive states is discussed.

Alpha-melanocyte stimulating hormone Lordosis Serotonin Quipazine Pirenperone

THE importance of peptides in the regulation of sexual behavior has become increasingly clear over the last decade. For example, prolactin [8], cholecystokinin [25], adrenocorticotropic hormone (ACTH) [7,66], beta-endorphin [50, 52, 64], gonadotropin releasing hormone [35, 46, 50, 52], corticotropin releasing hormone [51], and alpha-melanocyte stimulating hormone (MSH) [10, 45, 54–56, 66] have all been found to alter sexual behavior in the rat. The finding that a number of peptides alter sexual responding in the rat suggests that peptides are important modulators of reproductive states. MSH seems a particularly likely candidate for such a function in the rat for three reasons. First, when administered to a lateral ventricle, MSH produces both a short-term (same day) and a long-term (one week later) inhibition of lordosis ([45], but see [56]). Second, the work of Volosin and Celis [60–62] strongly suggests a role for MSH in the induction and/or maintenance of pseudo-pregnancy in the rat. Finally, MSH is known to play an important role in the stimulation of intrauterine growth of the fetus and placenta in the rat [18,53]. Thus, it is plausible that MSH is involved in the regulation of reproductive states in this species.

The next question, and the one addressed by the present series of experiments, concerns the mechanisms by which MSH may influence receptivity. It is generally agreed that serotonin plays an important role in the expression of receptivity. However, the discovery [42,43] that there exists more than one type of serotonin receptor suggests that the basic view of serotonin as inhibitory with respect to receptivity (e.g., [11, 12, 32, 63]) is too simplistic. Recent reports suggest more specifically that the traditionally observed inhibitory action of serotonin on receptivity is mediated by the serotonin type I_A receptor [1, 29, 31] while the more recently observed facilitatory action of serotonin appears to be mediated by the serotonin type II receptor [19, 26–28, 30, 65]. Thus, MSH could inhibit receptivity either by increasing serotonin type I_A activity or by decreasing serotonin type II activity. Lending plausibility to the notion that MSH may influence reproductive states (e.g., estrus, pseudo-pregnancy) through an interaction with serotonin are the findings that: (1) MSH decreases the binding of serotonin at serotonin type III binding sites [47], (2) the depletion of serotonin leads to a decrease in the concentration of MSH in the hypothalamus [13], and (3) serotonin [14, 34, 59] and MSH [9, 38, 40] are both located in brain regions (e.g., hypothalamus, septum, mesencephalic reticular formation) thought to be important in regulating reproductive states [2, 17, 23, 24, 49]. The present series of experiments was designed to examine the role of serotonin type II activity in the mediation of the short- and long-term inhibitory actions of MSH on receptivity.

GENERAL METHOD

SUBJECTS

Female Sprague-Dawley rats, obtained from the breeding

[1]This research was conducted by the author while at the University of British Columbia.
[2]Portions of this research were presented at the annual meeting of the Society for Neuroscience, Dallas, 1985.

colony in the Department of Psychology at the University of British Columbia, were used as subjects. Animals were housed individually in standard, wire mesh cages, under a reversed 12:12 hr light:dark cycle with food and water available ad lib.

PROCEDURE AND APPARATUS

Surgery and Histology

Chronic guide cannulae were implanted into the left lateral ventricle when subjects were approximately 70 days of age. Coordinates for cannula placement, taken from the atlas of Pellegrino, Pellegrino and Cushman [41], were as follows: A-P, −0.2; M-L, 1.5; D-V, −2.8. Bilateral ovariectomies and cannula implantation were performed with subjects under sodium pentobarbitol anesthesia (Somnitol, 0.8 ml/kg). Skull screws and dental acrylic were used to fix the cannula assembly in place. All subjects were employed in several experiments before histological verification of the implantation site was carried out. Because cannulae may shift slowly over time, the accuracy of cannula placement was assessed between experiments by measuring the latency to drink after the administration of 2 μg/4 μl angiotensin II, a potent dipsogen, via the cannula. Immediately after the injection, animals were returned to their cage. Animals that failed to drink within 30 sec were terminated as subjects. Upon termination as a subject, each animal was sacrificed and 4 μl of India ink was infused into the ventricle via the cannula to verify placement.

Drug and Hormone Treatments

Receptivity was induced by the subcutaneous (SC) administration of a single dose of 2 μg estradiol benzoate (EB) 48–51 hr before testing and a single dose of 200 μg progesterone (P) 4–7 hr prior to testing. EB and P were dissolved in 0.05 cc peanut oil. Unless otherwise noted, 200 ng MSH (in 4 μl sterile, 0.9% saline) was administered intracerebroventricularly (ICV) 4–7 hr prior to testing via an infusion pump at a rate of 1 μl/7 sec. These doses of estrogen, progesterone, and MSH had previously been employed and found effective in the current paradigm [44]. Quipazine was dissolved in saline and administered intraperitoneally (IP) at a dose of 3 mg/kg (concentration, 3 mg/0.4 cc) 1 hr prior to testing. This dose of quipazine has previously been found effective in attenuating the inhibitory actions of various serotonin type II antagonists [26,27]. Pirenperone was dissolved in a warm citrate solution and administered IP 1 hr before testing.

Behavioral Testing and Data Analysis

The lordosis response was used as the primary indicator of receptivity. Tests of sexual receptivity consisted of placing the female with a sexually vigorous male for a total of 10 mounts with pelvic thrusting. A lordosis quotient (LQ), the number of lordosis responses displayed by the female divided by the number of mounts by the male and multiplied by 100, was calculated for each subject. Sexually experienced animals were tested for receptivity at seven day intervals for a total of four tests. The first, third and fourth tests served as control tests, with no drug or peptide being administered. The second test occurred 3–5 hr after MSH administration and examined the short-term actions of MSH. Any drugs that were administered were administered 1 hr prior to testing on this day. The third test occurred 1 week after MSH administration and was used to examine the long-term action of MSH. Analyses of variance (ANOVAs) were used to analyze the data and significant effects were further examined by using the Newman-Keul's procedure with alpha set at 0.05.

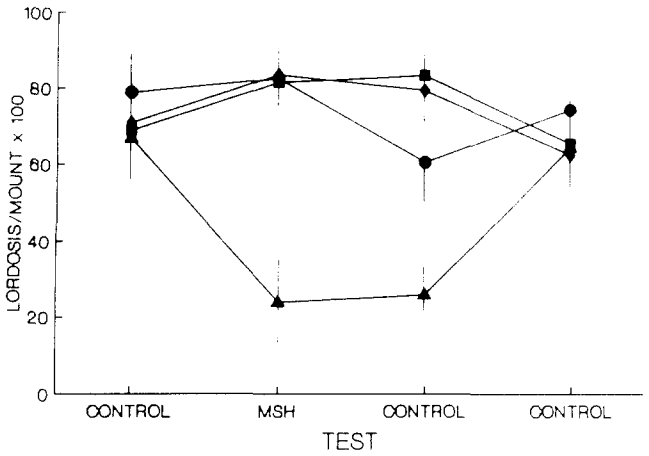

FIG. 1. Effects of quipazine on the MSH-induced inhibition of lordosis. Subjects received 2 μg estradiol benzoate 48–51 hr prior to testing and 200 μg progesterone 4–7 hr before testing. Tests occurred once per week for four weeks. Control tests occurred on Weeks 1, 3, and 4. MSH and quipazine were administered prior to testing during Week 2. MSH was administered to a lateral ventricle at a dose of 200 ng 4–7 hr prior to testing while quipazine was administered intraperitoneally at a dose of 3 mg/kg 1 hr prior to testing. ●: quip + MSH; ▲: saline + MSH; ◆: quip + saline; ■: saline.

EXPERIMENT 1

It is possible that the inhibitory action of MSH on lordosis is due, in part, to an MSH-induced antagonism of activity at serotonin type II receptors. If so, then the administration of a serotonin type II agonist should attenuate the effect. Quipazine, a relatively specific serotonin type II agonist [22, 48, 67], has been found to reverse the inhibition of receptivity produced by the administration of the serotonin type II antagonists pirenperone, pizotefin, cyproheptadine, and ketanserin [26,27]. If the inhibitory action of MSH is due, in part, to an antagonism of serotonin type II activity, then quipazine should be able to attenuate this effect. The first experiment was designed to examine this possibility.

METHOD

Subjects were assigned to one of four groups: saline + saline (n=14); saline + quipazine (n=14); MSH + saline (n=13); or MSH + quipazine (n=13).

RESULTS

An examination of the data suggests that MSH exerted both a short- and a long-term inhibitory action on lordosis. Quipazine appeared to fully attenuate the short-term action of MSH and partly attenuate the long-term action of MSH (see Fig. 1). An ANOVA indicated a significant effect of group, $F(3,150)=4.97$, $p<0.004$, and a significant group × test interaction, $F(9,150)=5.58$, $p<0.0001$. A Newman-Keul's analysis of the group × test interaction indicated that the mean LQs for the subjects receiving MSH on the day of

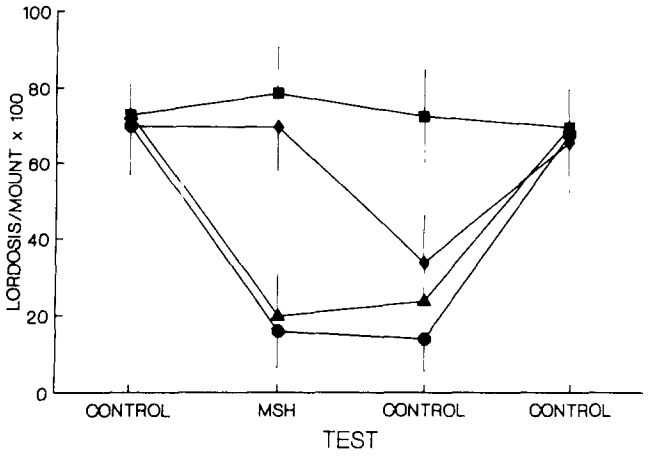

FIG. 2. Dose-response effects of MSH on lordosis. Subjects received 2 μg estradiol benzoate 48–51 hr prior to testing and 200 μg progesterone 4–7 hr prior to testing. Testing occurred once a week for four weeks, with control tests occurring during Weeks 1, 3, and 4. MSH was administered to a lateral ventricle 4–7 hr prior to testing during Week 2. ●: 100 ng MSH; ▲: 50 ng MSH; ◆: 20 ng MSH; ■: saline.

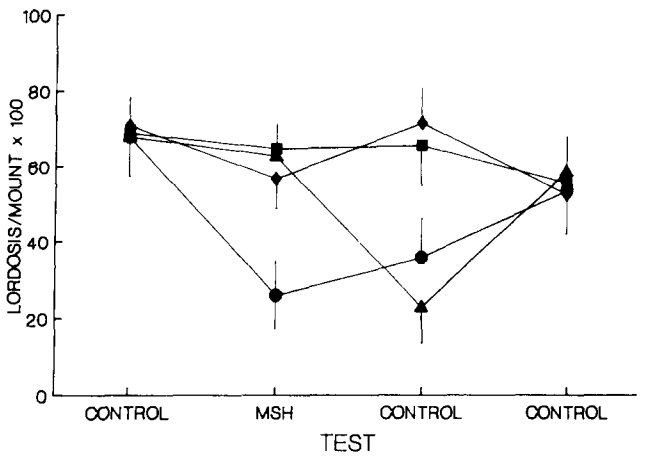

FIG. 3. Effects of subthreshold doses of MSH and pirenperone on lordosis. Subjects received 2 μg estradiol benzoate 48–51 hr prior to testing and 200 μg progesterone 4–7 hr before testing. Tests occurred once a week for four weeks, with control tests occurring during Weeks 1, 3, and 4. MSH and pirenperone were administered prior to testing during Week 2. MSH was administered to a lateral ventricle at a dose of 20 ng 4 hr prior to testing while pirenperone was administered intraperitoneally at a dose of 10 μg/kg 1 hr before testing. ●: pirenp + MSH; ▲: saline + MSH; ◆: pirenp + saline; ■: saline.

MSH administration and 1 week after MSH administration were significantly lower than all other mean LQs. Mean LQs for subjects receiving saline, quipazine, or MSH and quipazine did not differ significantly from each other.

EXPERIMENT 2

The results of Experiment 1 suggest that the short-term inhibitory action may be due, in part, to an MSH-induced reduction in serotonin type II activity. In addition, the finding that quipazine, when given on the day of MSH administration, partly attenuates the long-term action of MSH suggests that the short-term action of MSH on serotonin, when combined with other MSH effects, has long-term consequences. However, the possibility remains that both MSH and quipazine are acting upon some other neurotransmitter. A further verification of the importance of serotonin type II activity in mediating the inhibitory actions of MSH could be gained by the demonstration that lordosis is inhibited when subthreshold doses of MSH and a serotonin type II antagonist, such as pirenperone [16], are administered. Experiment 2 was designed to examine this possibility.

METHOD

Determination of Subthreshold Doses

Work by Mendelson and Gorzalka [27] suggests that the inhibitory action of pirenperone on lordosis is most likely due to the action of pirenperone on serotonin type II (versus dopaminergic) activity. Thus, pirenperone was selected for use in the present study. To determine the appropriate dose to employ in the present study, eight different doses of pirenperone were examined: 0, 2, 5, 10, 15, 25, 50, or 100 μg/kg. The concentration of pirenperone was varied such that the average volume injected was 0.12 cc. Results indicated that animals receiving 10 μg/kg pirenperone or less showed no inhibition of receptivity (mean LQ>80, $p>0.05$) while those receiving 15 μg/kg pirenperone or more showed a significant inhibition of receptivity (LQ <45, $p<0.05$). Thus, the 10 μg/kg dose was selected. Control animals received the saline + citrate vehicle.

To determine the dose of MSH to be administered, subjects were assigned to 1 of 4 groups: saline; 20 ng MSH; 50 ng MSH; 100 ng MSH. The standard 4-test paradigm was followed. Results indicated that 20 ng was below threshold for the short-term, but not the long-term inhibitory action of MSH (see Fig. 2). Since pirenperone was to be administered on the day of MSH administration, it seemed reasonable to employ a dose of MSH below threshold for the short-term effect; thus, the 20 ng dose was selected.

Experimental Procedures

Animals were assigned to 1 of 4 groups: ICV saline + IP saline with citrate (hereafter referred to as IP saline; n=14); saline + subthreshold pirenperone (n=14); subthreshold MSH + IP saline (n=12); subthreshold MSH + subthreshold pirenperone (n=12).

RESULTS

An examination of the data suggests that the subthreshold doses of MSH and of pirenperone did not inhibit receptivity when administered alone but did inhibit receptivity when administered in combination (see Fig. 3). An ANOVA revealed a significant effect of test, $F(3,144)=6.36$, $p=0.005$, and a significant group × test interaction, $F(9,144)=4.65$, $p<0.0001$. A Newman-Keul's analysis of the group × test interaction indicated that subjects receiving subthreshold doses of MSH + pirenperone were significantly less receptive than subjects receiving MSH, pirenperone, or saline on the day of MSH administration. In addition, subjects receiving MSH or pirenperone did not differ from those receiving saline on the day of MSH administration (Week 2). However, when tested in Week 3, subjects who had received MSH or MSH + pirenperone in Week 2 were significantly less receptive than subjects who had received pirenperone or saline in Week 2.

EXPERIMENT 3

The results of Experiments 1 and 2 suggest that the short-term action of MSH is due, in part, to an MSH-induced decrease in activity at serotonin type II receptors. However, pirenperone antagonizes both serotonin type II and adrenergic receptors [27,58]. Therefore, it is possible that the inhibition observed in Experiment 2 is due to a summation of effects at adrenoceptors rather than to a summation of effects of serotonin type II receptors. Quipazine appears to have little activity at adrenoceptors [48,67]. Thus, if quipazine was to reverse the inhibition produced by the co-administration of subthreshold doses of MSH and pirenperone, it would suggest that this effect is due to an inhibition of activity at serotonin type II receptors rather than to an inhibition of activity at adrenoceptors. The final experiment was designed to determine the effectiveness of quipazine in reversing the inhibitory effect produced by the co-administration of subthreshold doses of MSH and pirenperone.

METHOD

Subjects were assigned to 1 of 4 groups: IP saline with citrate (hereafter referred to as IP saline) + ICV saline (n=14); IP saline + subthreshold pirenperone and MSH (n=11); quipazine + ICV saline (n=13); quipazine + subthreshold pirenperone and MSH (n=12). Doses and times of MSH, pirenperone, and quipazine administration followed those used in Experiment 2 (MSH and pirenperone) and Experiment 1 (quipazine).

RESULTS

An examination of the data suggests that quipazine fully attenuated the short-term inhibitory action produced by the co-administration of subthreshold doses of pirenperone and MSH but did not attenuate the long-term action of MSH (see Fig. 4). In addition, quipazine appeared to have facilitated receptivity in subjects receiving quipazine alone. An ANOVA revealed a significant group × test interaction, $F(9,138)=5.34$, $p<0.0001$. A Newman-Keul's analysis revealed that, on the day of drug administration (Week 2), subjects receiving pirenperone and MSH were significantly less receptive than subjects in the remaining three groups. In addition, subjects receiving quipazine were significantly more receptive than subjects receiving saline or quipazine + pirenperone and MSH. When tested in Week 3, subjects who had received either pirenperone and MSH or quipazine + pirenperone and MSH in Week 2 were found to be significantly less receptive than subjects who had received either saline or quipazine in Week 2.

GENERAL DISCUSSION

The results of the present series of experiments strongly suggest that MSH-induced alterations in activity at serotonin type II receptors are involved in the manifestation of both the short- and the long-term effects of MSH. In Experiment 1, quipazine, when administered on the day of MSH administration, was found to significantly attenuate the short- and the long-term action of MSH. Quipazine, when administered alone, did not significantly facilitate receptivity. The results of Experiment 2 indicated that the effects of subthreshold doses of MSH and of pirenperone could summate to produce an inhibition. It was of interest to note that 20 ng MSH failed to produce a short-term inhibition of receptivity although it did produce a long-term inhibition of receptivity. In the final experiment, quipazine was found to significantly attenuate the short-term, but not the long-term inhibitory action produced by the co-administration of subthreshold doses of MSH and pirenperone. Quipazine was also found to significantly facilitate receptivity.

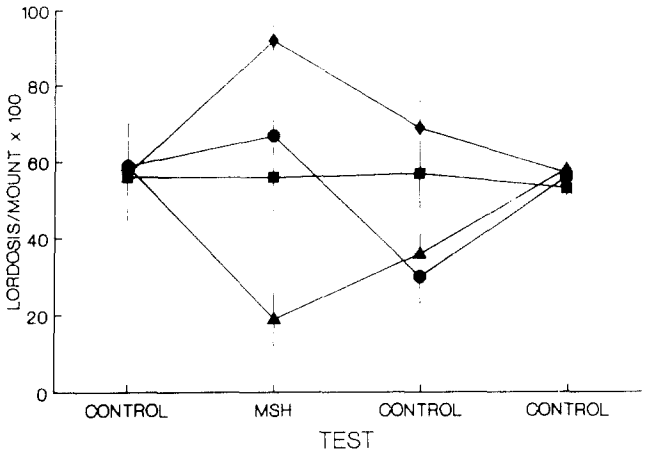

FIG. 4. Effects of quipazine on the inhibition of lordosis produced by the co-administration of subthreshold doses of MSH and pirenperone. Subjects received 2 μg estradiol benzoate 48–51 hr prior to testing and 200 μg progesterone 4–7 hr before testing. Testing occurred once a week for four weeks. Control tests were given during Weeks 1, 3, and 4. MSH, quipazine, and pirenperone were administered prior to testing during Week 2. MSH was administered to a lateral ventricle at a dose of 20 ng 4 hr prior to testing while pirenperone (10 μg/kg) and quipazine (3 mg/kg) were administered intraperitoneally 1 hr prior to testing. ●: pirenp + MSH + quip; ▲: pirenp + MSH; ◆: quip + saline; ■: saline.

The facilitatory action of quipazine on receptivity and the failure of quipazine to significantly attenuate the long-term action of MSH in Experiment 3 contrasts with the results of Experiment 1. It is possible that the failure to observe a facilitatory effect of quipazine on receptivity in Experiment 1 was due to the high degree of receptivity already displayed by the subjects (mean LQ ≈80). The mean LQ of subjects in Experiment 3 was somewhat lower (≈59) and thus, any facilitatory effect of quipazine may have been more obvious. In Experiment 3, the failure to observe a significant attenuation of the long-term action of MSH by quipazine may have been due to several factors. First, quipazine is a type II agonist while pirenperone is a type II antagonist; their co-administration could result in one drug effectively cancelling out the other. Second, the relative size of the MSH-induced inhibition in Experiment 3 was less than in Experiment 1. Thus, a partial attenuation of quipazine of the long-term effect may have been less apparent. A third possibility is that the non-serotonergic components of the long-term effect of MSH were more prevalent in Experiment 3 than in Experiment 1.

It could be argued that problems with drug specificity make premature the conclusion that the inhibitory action of MSH involves changes in serotonin type II activity. For example, pirenperone has antagonistic actions at both serotonin type II receptors and at alpha-adrenoceptors [58]. Thus, the inhibition of receptivity observed in Experiments 1–3 might be due to the effects of MSH and pirenperone on alpha-adrenoceptors rather than on serotonin type II recep-

tors. The attenuation of the effects of MSH and of pirenperone by quipazine, which has little adrenergic activity [48,67], makes this explanation unlikely. However, MSH has been reported to influence the metabolism of dopamine in the rat brain [21] and may influence other neurotransmitters as well. Thus, it is important that future experiments employ drugs (e.g., ketanserin) that have similar sites of action but somewhat different pharmacological profiles.

The short-term alterations in activity at serotonin type II receptors that appear to be produced by MSH may also play a role in the long-term action of this peptide. In Experiment 1 quipazine partially attenuated the long-term action of MSH. In Experiment 3, this effect was not observed, possibly because pirenperone antagonized the action of quipazine. Furthermore, earlier work [44] suggests that parachlorophenylalanine, when administered 72 hr prior to MSH (to ensure maximal depletion of serotonin [20]), may prevent the long-term action of MSH. Thus, it would appear that a short-term, MSH-induced decrease in serotonin activity may be a necessary, but not a sufficient, prerequisite for the long-term action of MSH on receptivity.

It is of interest to note that the mechanism mediating the long-term effect of MSH appears to be more sensitive to MSH than the mechanism mediating the short-term effect (Fig. 2). This difference plus the implication that serotonin activity is differentially important in the production of the short- and long-term actions of MSH suggests that the short- and long-term actions of MSH may serve different purposes. The research of Volosin and Celis [60,62] indicates that cervical stimulation, such as that experienced during copulation, can lead to the release of MSH in the rat. As serum MSH levels were measured, the effect of cervical stimulation on levels of MSH in the brain remains to be determined. However, research suggests that MSH from the pituitary may reach the brain via retrograde transport through the portal blood vessels [33,39]. Thus, even if cervical stimulation failed to lead to the release of MSH within the brain, such stimulation could still lead to increased levels of brain MSH. This increase in brain MSH may then inhibit activity at serotonin type II receptors, resulting in a short-term decrease in receptivity.

The apparent long-term inhibitory action of MSH may be related to the ability of MSH to induce and/or maintain pseudopregnancy and may, in some way, relate to pregnancy as well. Furthermore, the long-term action of MSH may be a consequence of the short-term actions of MSH on serotonin and other neurotransmitters. For example, a short-term, MSH-induced decrease in serotonin type II activity may lead to a longer-term decrease in estrogen and/or progestin receptors. Research on the influence of changes in serotonin activity on estrogen and/or progestin receptor density is sparse. However, there is a reasonable amount of evidence that alterations in neurotransmitter availability influence estrogen and/or progesterone binding in the cytoplasm and nucleus of target neurons (e.g., [4, 5, 15, 36, 57]). The plausibility that the long-term action of MSH is produced, in part, by a decrease in estrogen and/or progestin receptors is increased by past [44] and ongoing research. This research suggests that the long-term action of MSH is significantly attenuated if the dose of progesterone administered on the day of long-term testing is increased from 200 μg to 500 μg. Increasing the dose of progesterone administered is known to attenuate the inhibition of receptivity (also seen in pseudopregnancy) that occurs after the down-regulation of progestin receptors [3,6]. Thus, the long-term inhibitory action of MSH may be a result of an MSH-induced decrease in progestin receptors.

When the above information is combined, a plausible, testable model of MSH action on receptivity emerges: an MSH-induced, short-term inhibition of serotonin activity inhibits lordosis and, when combined with the effects of MSH on other neurotransmitters, results in a longer-term decrease in estrogen and/or progestin receptors. This decrease in estrogen and/or progestin receptors is then manifested as a decline in receptivity. At present, this model of MSH action is largely speculative and requires extensive physiological and behavioral testing before it can be verified. However, the possibilities are intriguing and additional research, whether or not it supports the current model, will undoubtably enhance our understanding of the regulation of reproductive states.

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