DECREASED ALLOPREGNANOLONE INDUCED BY HORMONAL CONTRACEPTIVES IS ASSOCIATED WITH A REDUCTION IN SOCIAL BEHAVIOR AND SEXUAL MOTIVATION IN FEMALE RAT

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INTRODUCTION

Allopregnanolone is a neuroactive steroid, produced in the periphery and directly in the brain from progesterone, which exerts a rapid and specific neurobiological effect. The predominant mechanism action of allopregnanolone involves the expression of GABA-A receptors, which is a major inhibitory neurotransmitter in the brain. It has been shown that it can facilitate social and sexual behavior of rodents, which are further increases in brain allopregnanolone concentrations. Therefore, systemic or local allopregnanolone administration in the hypothalamus or midbrain, promotes social, affective and positive behaviors, while blocking progesterone metabolism through a 5a-reductase inhibitor, reduces proceptivity and receptivity compared to control animals. We have previously demonstrated that chronic treatment with a combination of estradiol (EE) and levonorgestrel (LNG), two of the components of most of the oral contraceptives, significantly reduces plasma levels of allopregnanolone in female rats, induce a decrease in brain and plasma concentrations of allopregnanolone. So, we have examined whether the reduction in the concentrations of allopregnanolone induced by EE-LNG treatment was associated with a modification of the social and sexual behavior of rats.

MATERIALS AND METHODS

Animals and treatments - Adult female Sprague-Dawley rats weighing 200-250 g and 6-month-old were housed in a temperature-controlled room (22 ± 1°C). The lighting cycle was 12:12 h light/dark (lights on at 07:00 h) and ad libitum food and water were available throughout the study. The estradiol valerate (EE) and levonorgestrel (LNG) were dissolved in oil (vehicle) and were administered for 10 days. Animals were randomly assigned to one of the following groups: (1) control (vehicle); (2) EE (60 μg/kg/day); (3) LNG (50 μg/kg/day); (4) EE-LNG (60 μg/kg/day and 50 μg/kg/day, respectively). Animals were sacrificed by cervical dislocation 1 h after the last treatment.

Proceptive behaviors (n) were expressed as the number of mounts (intromissions) per intruder test, as described previously. For the assessment of lordosis behavior, animals were mounted daily with an estrous female (residents) at a ratio of 5:1, while the hormone-treated animals were mounted by the same estrous females. The percentage of lordosis was measured as described previously.

RESULTS

3 EFFECT OF LONG-TERM TREATMENT WITH EE-LNG ON THE BEHAVIOR OF RATS IN THE NOVICE MATING TEST

4 EFFECT OF LONG-TERM TREATMENT WITH EE-LNG ON THE BEHAVIOR OF RATS IN THE PACED MATING TEST

5 EFFECT OF LONG-TERM TREATMENT WITH EE-LNG ON THE BEHAVIOR OF RATS IN THE PACED MATING TEST

6 EFFECT OF ESTRADIOL AND PROGESTERONE ADMINISTRATION ON THE BEHAVIOR OF EE-LNG-TREATED RATS IN THE PACED MATING TEST

7 EFFECT OF FINASTERIDE ADMINISTRATION ON THE BEHAVIOR OF EE-LNG-TREATED RATS IN THE PACED MATING TEST

8 CONCLUSIONS

EE-LNG-treated rats showed significant decreases in dominant and social behaviors in the resident-intruder paradigm. Given that these behaviors are dependent upon the homeostatic fluctuations of the estrous cycle, our results may be related to the lack of these fluctuations induced by EE-LNG. The administration of finasteride, a 5α-reductase inhibitor, did not affect the behavior of rats in the paced mating test or the microdialysis allopregnanolone concentrations, while progesterone treatment resulted in significant increases in both receptivity and proceptivity. This could be related to the recovery of brain concentrations of allopregnanolone induced by progesterone administration. The administration of finasteride, alone or in combination with progesterone, resulted in a significant decrease in proceptive behavior with respect to P-treated rats, and in a drastic reduction of allopregnanolone concentrations, while it did not alter progesterone levels. This result suggests that allopregnanolone is necessary for the expression of proceptive behaviors, and its low levels are responsible for the reduction of sexual motivation in EE-LNG-treated rats.

REFERENCES