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Estradiol and progesterone regulation of neural circuits controlling reproduction

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In rodents, female reproductive behavior is strongly influenced by estradiol (E2) and progesterone (P) whose levels fluctuate during the cycle. P and E2 work in synergistic fashion to facilitate female receptivity. Some neural circuits implicated in the control of sexual behavior and/or reproductive physiology (the nitrergic and the kisspeptin systems) also show changes during the estrous cycle. Nitric oxide (NO) is a gaseous neurotransmitter playing an important role in the regulation of sexual behavior in rodents. NO is produced by the enzyme neural NO synthase (nNOS) whose expression is influenced by gonadal hormones. The kisspeptin system (clustered in two groups of cell bodies in the periventricular region, RP3V and in the arcuate nucleus, ARC) is also modulated by gonadal hormones during the cycle and sends fibers mainly to the GnRH neurons and in a few other locations, including the paraventricular nucleus, PVN. Previous studies were unable to distinguish among the role played by P or E2 in inducing these changes. In the present study, we investigated the effects of E2 and P (alone or together) on the neural circuits of gonadectomized female mice, following a timing of administration that emulates the different phases of estrous cycle, for two cycles of 4 days.

The quantitative analysis of nNOS-ir system demonstrated a statistically significant variation in the number of positive cells in the bed nucleus of the stria terminalis, the arcuate nucleus and the medial preoptic area, with the highest number of positive neurons observed in E2 + P group. In physiological conditions, the two main groups of kisspeptin neurons respond in different way to the fluctuations of E2: the highest expression being in estrus in RP3V and PVN (positive feedback), and during the diestrus in ARC (negative feedback). As expected, the two cell groups were differentially affected by E2; the RP3V group was positively influenced by E2 (alone or with the P), whereas in the ARC the administration of E2 did not affect the system. However P (alone) induced a rise in the kisspeptin immunoreactivity. All the treatments significantly affected the kisspeptin innervation of the PVN, with regional differences, suggesting that these fibers arrive from both RP3V and ARC nuclei.

In conclusion, our data suggest that, in addition to E2, also P may have an important role in the regulation of neural circuits controlling reproductive behavior.

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