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SESSION 1

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The hypothalamic control of the menstrual cycle

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(*Abstract*)

Despite the limited amount of direct evidence for the primate, it is now quite certain that the menstrual cycle lies under neural control. The importance of emotional and psychogenic factors in altering gonadotrophin secretion in human females needs no emphasis, while in lower primates smell may be significant: male monkeys rendered anosmic lose their sexual drive. The chemical agents involved are called pheromones and their action in mice has been closely studied. In some laboratory species, the length of day greatly influences sexual rhythmicity and reproductive activity, but the pathways through which olfactory or visual stimuli affect pituitary function are not well understood. However, hypothalamic nuclei are involved and the way in which the anterior pituitary gland is controlled is well documented.

The median eminence of the hypothalamus produces neurohumoral agents or releasing factors which travel through the hypophysial portal vessels to alter the output of the appropriate trophic hormone. Active extracts of the median eminence have been prepared which affect the secretion of each pituitary hormone. Most commonly, the output of hormone is increased but that of prolactin is inhibited, so that damage to the median eminence, or pituitary stalk section, which abolishes release of the neurohumors, favours prolactin secretion. It has proved difficult to separate the agents controlling the output of follicle-stimulating hormone and luteinizing hormone, but they are active in minute quantity. The injection of a few micrograms of pig luteinizing hormone releasing factor into normal men or women has elevated the serum gonadotrophin level to between two and seven times the control level, with the peak concentration being reached about 25 min after injection. Portal vessel blood has been collected in rats and the content of gonadotrophin releasing factor appears to vary in phase with the oestrous cycle. As yet, the structure only of thyrotrophin releasing factor has been determined, but the others appear to be short chain polypeptides.

If the pituitary stalk is sectioned surgically, and regeneration of the portal vessels prevented, gonadotrophin releasing factors fail to reach the anterior pituitary, gonadotrophin secretion falls and gonadal atrophy follows. However, if instead of isolating the pituitary from the hypothalamus, the hypothalamus is separated surgically from the rest of the brain, gonadotrophins continue to be secreted. Such observations, as well as others based on the effects of localized electrical stimulation of, or damage to, the hypothalamus, or the implantation of pars distalis tissue therein, lead to the conclusion that the basal hypothalamus supports the low, constant, production of gonadotrophin, while a drive toward the cyclic surge of neurohumor release necessary to enhance gonadotrophin secretion and so cause ovulation originates in the pre-optic area. That is the general view: some recent work with guinea-pigs and rats nevertheless indicates that disconnection of the median eminence from the pre-optic area is compatible with continued ovulation.

In view of its role in the generation of cyclic ovulation it is perhaps to be expected that the pre-optic area is involved in the sexual differentiation of gonadotrophin secretion. Developmentally, androgen produced by the foetal testis acts on this region to abolish cyclic activity, so that production of gonadotrophin proceeds at a constant rate. Appropriately, ovarian cycles in genetic females can be permanently abolished by the administration of androgen at the appropriate stage of foetal development. The application of minute amounts of testosterone to the pre-optic area of newborn rats stops the regular ovulation expected after sexual maturation.

Since the activities of the hypothalamus in

controlling gonadotrophin secretion are affected by the rest of the brain, it is of interest to determine which areas are of greatest significance. The response to emotional changes indicates that the cerebral cortex is concerned; indeed, hypertonic saline applied to the cortex in rats has caused ovulation. However, complete removal of the cerebral cortex leaves cyclic ovarian activity unimpaired. The limbic system unquestionably affects ovarian function and it seems that its prime components, the amygdala and hippocampus, exert antagonistic influences in that the amygdaloid nuclei are believed to stimulate the secretion of gonadotrophin, while the hippocampus inhibits such activity. Stimulation of the amygdaloid nuclei has caused ovulation in several species while, in rats, stimulation of the hippocampus just before excitation of the amygdala reduced the discharge of gonadotrophin. In monkeys, bilateral temporal lobectomy or destruction of the amygdaloid nuclei has disturbed the menstrual cycle and caused amenorrhea, but no consistent pattern of change has been produced.

In all discussions of the control of sexual function the feedback action of the gonadal steroids on the brain looms large. This has been studied by giving labelled steroids to animals and studying their uptake by the brain, by applying steroids directly to the brain, and by looking at the changes in the electrical activity of the brain caused by gonadal hormones. Stimulatory and inhibitory effects of steroids on brain function have been followed in this way and related to the production and inhibition of ovulation, but there is increasing evidence for a direct action of oestrogen and progesterone upon the cells of the anterior pituitary.