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Barraclough C A & Gorski R A. Evidence that the hypothalamus is responsible for androgen-induced sterility in the female rat. *Endocrinology* 68:68-79, 1961.
[Department of Anatomy, School of Medicine, University of California, Los Angeles, and Research Division, Veterans Administration Hospital, Sepulveda, CA]

This paper describes studies on hypothalamic function in the androgen-sterilized rat and the experiments that led to our postulating that a dual hypothalamic control of gonadotropin secretion exists. [The *SCI*® indicates that this paper has been cited in more than 460 publications.]

The Inherently Feminine Brain

Charles A. Barraclough
Department of Physiology
School of Medicine
University of Maryland
655 West Baltimore Street
Baltimore, MD 21201

In 1936, C.A. Pfeiffer[1] observed that if male rats were castrated between birth and three days of life and ovarian tissue was transplanted into such animals in adulthood, corpora lutea (CL) formed in these ovaries, suggesting that ovulation had occurred. He interpreted these results to mean that a hormone-dependent sex difference in pituitary function was produced by neonatal gonadal secretions.

As a graduate student with James Leathem at Rutgers University, New Jersey, we decided to evaluate the effect of testosterone, given as a single injection at different prepubertal ages (5, 10, 20 days of life), on subsequent development of the male and female reproductive systems. We observed that if androgen was injected before the 10th day of life, all mice, when adult, had polyfollicular ovaries that lacked CL. These initial studies established that a critical period existed during the development of the hypothalamo-hypophyseal-ovarian axis during which exposure to androgen produced permanent sterility.[2]

After completing my postdoctoral neuroendocrine training with Charles H. Sawyer at the University of California at Los Angeles, I repeated my earlier mouse work in female rats with equivalent results. All rats treated with androgen before the 10th day of life were permanently sterile as adults, and I named this animal model the androgen-sterilized rat (ASR).[3]

About this time, Vaughn Critchlow, a student with Sawyer, showed that electrical stimulation of specific hypothalamic regions induced ovulation in proestrous rats. Using this method, Roger A. Gorski (a graduate student) and I examined whether neonatal androgen treatment deleteriously affected the hypothalamus. We observed that ovulation occurred in ASR only after stimulation of the medial basal hypothalamus but not when the preoptic area was activated. Based on these observations, we proposed that "cyclic" and "tonic" regions exist within the hypothalamus that control gonadotropin secretion. We suggested that the cyclic control of preovulatory luteinizing hormone (LH) surges resided within the preoptic area, and the tonic control of gonadotropin secretion was located within the medial basal hypothalamus. In 1961, we had no idea that luteinizing hormone releasing hormone (LHRH) existed, nor did we know the hypothalamic location of LHRH neurons. Moreover, it was not possible to measure steroids or gonadotropins in plasma during these years.

The description of this animal model and the hypothesis of a dual hypothalamic control of gonadotropin secretion resulted in literally thousands of subsequent studies by laboratories throughout the world. For many functional activities, the brain is inherently feminine, or at least undifferentiated. Functional characteristics considered typical of the male are imposed by the masculinizing and defeminizing action of testicular hormones. In fact, it is now clear that gonadal hormone-determined structural sex differences exist in the brain, including the preoptic area.[4]

While the site(s) and mechanisms by which androgen (estrogen) permanently affects neuronal processes regulating preovulatory LH surges remains unresolved, some progress is being made. For example, colleagues and I have shown that significant increases in hypothalamic norepinephrine secretion are essential for preovulatory LH surges to occur, and, in ASR, this effect is absent.[5] Some *Citation Classics* presumably resolve an issue; this one helped open a scientific question that still remains unanswered.

1. **Pfeiffer C A.** Sexual differences of the hypophyses and their determination by the gonads. *Amer. J. Anat.* 67:195-225, 1936. (Cited 370 times since 1945.)
2. **Barraclough C A.** Influence of age on the response of preweaning female mice to testosterone propionate. *Amer. J. Anat.* 93:493-522, 1955. (Cited 20 times.)
3. ----------. Production of anovulatory sterile rats by single injections of testosterone propionate. *Endocrinology* 68:62-7, 1961. (Cited 440 times.)
4. **Gorski R A, Harlan R E, Jacobson C D, Shryne J E & Southam A M.** Evidence for the existence of a sexually dimorphic nucleus in the preoptic area of the rat. *J. Comp. Neurol.* 193:529-39, 1980. (Cited 165 times.)
5. **Lookingland K J & Barraclough C A.** Failure of the hypothalamic noradrenergic system to function in adult androgen-sterilized rats. *Biol. Reprod.* 27:268-81, 1982. (Cited 30 times.)

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