An Overview of FSH Regulation and Action

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Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are the two anterior pituitary hormones that control gonadal function. Of the two, LH has been much more extensively studied, due in large part to the earlier development of a sensitive radioimmunoassay (RIA) for LH. Much of what is known about the regulation of FSH synthesis and secretion has been extrapolated from studies of LH. This approach was initially considered valid because both hormones are synthesized and secreted by the same pituitary cells (1, 2) and because a single hypothalamic hormone, gonadotropin releasing hormone (GnRH), has been shown to influence both (3, 4). Despite these important similarities, our understanding of gonadotropin regulation might have been quite different today if we had based it on an equally intensive study of FSH.

CNS Regulation of FSH Secretion

Hypothalamic Regulation

Although GnRH is capable of stimulating both LH and FSH release and synthesis, it exerts much tighter control over LH than FSH secretion and synthesis, thus lending credence to speculation about the existence of a separate FSH releasing factor (FSHRF). There are still two schools of thought on this matter, although evidence that GnRH is the only hypothalamic releasing hormone controlling gonadotropin secretion is mounting.

Early studies showed that exogenous GnRH stimulates both LH and FSH release in vivo (5, 6); however, different GnRH infusion patterns favor one or the other gonadotropin. Slow infusion of GnRH favors FSH release over LH release (7–9); indeed, in rats very slow infusion can selectively stimulate FSH release (10). When endogenous GnRH secretion is elicited by electrical
stimulation of the medial preoptic area (MPOA), high-intensity, high-frequency stimulation, which activates more MPOA tissue, favors LH pulses, and low-intensity, low-frequency stimulation favors FSH (10). Similarly, low-frequency exogenous GnRH pulses administered to hypothalamic-lesioned ovariectomized female monkeys increase FSH secretion selectively (11). Further evidence that FSH is less GnRH dependent than LH derives from experiments using NMA (N-methyl-D-aspartate), an analog of the excitatory amino acid aspartate. NMA stimulates GnRH secretion and thus elicits LH, but not FSH, release in intact male and female rats (12, 13), while it stimulates both in monkeys (14).

GnRH also elicits FSH release and synthesis in vitro, but LH is stimulated to a much greater extent. Increasing concentrations of GnRH stimulate FSH release up to 5-fold and LH up to 100-fold (15, 16). Hourly stimulation of pituitary fragments in a dynamic perfusion system with pulses of GnRH elicits pulses of FSH and LH from pituitaries of intact and gonadectomized male and female rats in a dose-dependent manner (17, 18).

LH and FSH responses to GnRH antagonists and antisera also differ. GnRH antagonists or antisera maximally reduce immunoreactive FSH by only 30%-60% in castrates of both sexes after 12 h, while LH drops by 80% within 2 h and by 90% within 5 h (19-24). Superimposing inhibin on GnRH antagonist treatment further suppresses FSH to intact levels (25). Certain circulating isoforms of FSH, which are induced by GnRH antagonist administration, have been found to possess anti-FSH activity (26). Superimposing testosterone (T) or dihydrotestosterone (DHT), but not estradiol (E), on long-term GnRH antagonist treatment in intact and orchidectomized rats prevents or slows the declines in serum and pituitary FSH caused by antagonist alone, indicating a stimulatory effect of T on FSH synthesis that is independent of GnRH (27, 28).

Further evidence that FSH is not dependent upon minute-to-minute regulation by GnRH pulses comes from studies measuring pulsatile hormone secretion. LH is released in a pulsatile manner in intact and gonadectomized rats, with pulse frequency and amplitude increasing after gonadectomy (29-32). FSH secretion in intact rats also appears to be pulsatile; however, the pulses are much more variable in amplitude and frequency (33, 34). After gonadectomy the FSH pulse frequency does not attain the high values that LH pulse frequency reaches (Fig. 1.1) (33-35).

Assuming that each LH pulse reflects a preceding GnRH pulse, these data imply that a GnRH pulse frequently is not followed by an FSH pulse. Use of the push-pull perfusion technique to measure GnRH output from the hypothalamus demonstrates a high correlation between GnRH pulses and serum LH, but not FSH, pulses in male rats (33). Lumpkin et al. (35) found that 83% of FSH pulses in ovariectomized rats coincided with LH pulses; however, they also noted that since many more LH than FSH pulses were