Regular reproductive cycles cease relatively early in the life span of many female mammals. The age-associated loss of reproductive fertility has been well characterized in the female rat (1–5). Female rates typically cease exhibiting regular 4–5-day estrous cycles by 10–12 months of age (1,2). As female rats age, regular estrous cycles may be replaced by lengthened cycles, irregular cycles, and, finally, by an acyclic state. Evidence of alterations in the function of the reproductive axis, particularly in patterns of gonadotropin secretion, have been documented in female rats prior to detectable disturbances in regular estrous cycles. These subtle but measurable changes effectively herald the beginning of age-related alterations within the hypothalamic–pituitary–ovarian axis. Although age-related deficits have been identified at all levels of the reproductive axis (1), there is considerable evidence to suggest that alterations at the hypothalamic level are particularly important to the reproductive decline with age in this species (2–5).

Alterations in Circulating Hormone Levels in Aging Female Rats

Numerous studies have documented altered gonadotropin secretion with age (for review, see Refs. 1–4,6). Before the cessation of estrous cyclicity in rats, the preovulatory luteinizing hormone (LH) surge on proestrus is typically attenuated in magnitude and may also be delayed in time. In addition, the elevation in LH levels in response to ovariectomy is significantly reduced, and the steroid-induced LH surge is also diminished in ovariectomized middle-aged relative to young females. The data currently available suggest
that aging rats have a diminished capacity for LH release that may ultimately be responsible for the loss of estrous cyclicity in this species.

Alterations in circulating steroid levels have also been observed in middle-aged cycling females. Estradiol levels are increased on the day of proestrus in middle-aged rats (6). In contrast, age-related deficits in progesterone secretion have been observed in female rats and mice, and contribute to the increase in the estradiol–progesterone ratio that characterizes aging in females of both species (1). This elevated estrogen–progesterone ratio may promote the loss of estrous cycles by interfering with normal feedback mechanisms or by desensitizing the reproductive axis to the actions of estradiol (1,2). The intricate interrelationships between gonadotropin secretion and gonadal steroid production make it difficult to determine the degree to which the well-documented age-related changes in gonadotropin secretion contribute to the altered steroid hormone levels noted in middle-aged females prior to the loss of estrous cyclicity.

**LHRH Regulates Pituitary Gonadotropin Synthesis and Secretion**

LHRH (also known as gonadotropin-releasing hormone, GnRH) is the primary hypothalamic signal known to regulate pituitary gonadotropin synthesis and secretion. It is likely, therefore, that the well-documented alterations in gonadotropin secretion in middle-aged female rats reflect, to some degree, age-related changes in the parameters of LHRH secretion from the hypothalamus. For this reason, much research in our lab has focused on the examination of LHRH neuronal function in middle-aged female rats.

The parameters of LHRH secretion reflect the exquisite orchestration of a large number of signals that originate from within the hypothalamus and from other regions of the brain and brainstem (7). The changes in the pattern of LHRH release in conjunction with the preovulatory or steroid-induced LH surge in this species is dependent upon the precise coordination of a vast array of signals extrinsic to the LHRH neurons as well as increased activity of the subset of LHRH neurons that participate in LH surge induction. Parameters of LHRH secretion provide a barometer of hypothalamic function and may also reflect the functional integrity of the population of LHRH neurons in aging females.

**LHRH Neurons Are Dispersed Throughout the Basal Hypothalamus**

LHRH neurons are diffusely distributed within the basal forebrain (8). The majority of the widely distributed population of LHRH cell bodies project to the median eminence (9). There, LHRH is released into the pituitary por-