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JOURNAL ARTICLE

Age-related decrease in hypothalamic gonadotropin-releasing hormone (GnRH) gene expression, but not pituitary responsiveness to GnRH, in the male Brown Norway rat

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As is the case in humans, aging male Brown Norway (BN) rats exhibit both primary and secondary (hypothalamic/pituitary) testicular failure. We hypothesized that secondary testicular failure in aging BN rats is due to alterations in both hypothalamic and pituitary function. In order to determine whether gonadotropin-releasing hormone (GnRH) gene expression is altered with aging, we compared hypothalamic preproGnRH (ppGnRH) mRNA by in situ hybridization histochemistry and GnRH peptide content in microdissected brain areas by radioimmunoassay in intact (or sham-operated) young, middle-aged, and old male rats. In addition, we determined hypothalamic-pituitary responsiveness to the removal of testicular feedback by comparing ppGnRH messenger RNA (mRNA) and gonadotropin levels in sham-operated and orchidectomized young, middle-aged, and old rats. In sham-operated rats, both the cellular ppGnRH mRNA content and the number of neurons expressing ppGnRH mRNA were lower in old compared with young and middle-aged rats. In addition, GnRH content decreased with aging in intact rats in 2 of the 3 brain areas examined, and GnRH content tended to decrease with aging in the third region. Morning serum luteinizing hormone (LH) levels were unchanged with aging, whereas follicle-stimulating hormone (FSH) was significantly increased in old compared with younger intact rats. The cellular ppGnRH mRNA content also decreased with aging in orchidectomized rats, although the number of neurons expressing ppGnRH mRNA was unchanged with aging in these rats. Within age groups, the cellular ppGnRH mRNA content was higher in orchidectomized than in sham-operated rats, though there was no effect on the number of neurons expressing GnRH. In a second study, we compared pituitary responsiveness to GnRH by measuring serum LH and FSH levels after GnRH administration in intact BN rats of different ages. The LH response to GnRH was unchanged with aging, whereas the FSH response to GnRH tended to increase with aging. Despite similar LH responses, the testosterone (T) response to GnRH declined progressively with aging. A third study assessed age-related changes in the circadian rhythm of circulating LH, T, and corticosterone (B) levels. LH levels over a 24-hour period decreased with aging and tended to be lower in the morning hours in all age groups, and circadian rhythmicity was blunted in middle-aged and old compared with young rats. T levels over 24 hours declined progressively with aging, and these levels showed a bimodal diurnal variation in young rats, a variation that was not evident in older animals. B levels

over a 24-hour period were lower in old than in younger animals, and with aging, there was dampening of the amplitude of the circadian rhythm of B. Taken together, these findings suggest that secondary testicular failure in aging male BN rats is due in part to decreased GnRH gene expression rather than to decreased pituitary responsiveness to GnRH. This reduction in GnRH gene expression with aging is not dependent on testicular feedback factors. Finally, the blunted circadian rhythmicity of LH and T secretion with aging provides further evidence of altered hypothalamic regulation of gonadal hormone secretion in old animals.

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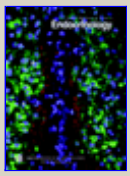

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