Reproductive Aging and the Human Hypothalamus

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The goal of our laboratory in the 1990s has been to characterize the molecular events that occur in the human hypothalamus in response to menopause. Despite the major clinical significance of menopause on a growing proportion of our society, there have been few studies of the aging human hypothalamus. In addition, from a basic science perspective, menopause provides a unique opportunity to study hypothalamic control mechanisms in the human. Decades of animal research have also provided a rationale for focusing on specific hypothalamic systems and neuronal populations. Finally, the development of in situ hybridization technology has allowed the measurements of cellular levels of mRNAs in human postmortem material with the precision achieved in laboratory animals. As a result, we have been able to provide some of the first descriptions of changes in neuronal morphology and neuropeptide gene expression in the hypothalamus of postmenopausal women.

Alterations in peripheral plasma hormone levels in postmenopausal women are consistent and dramatic. The loss of ovarian follicles (1) results in castrate levels of ovarian steroids (2). Because of removal of steroid negative feedback on the pituitary and hypothalamus, gonadotropins are significantly increased in peripheral plasma (3–5). This rise in plasma gonadotropins is similar in magnitude to that seen after ovariectomy in young women (6–8). Indeed, ovariectomy in young women is commonly referred to as “surgical menopause” (9).

More than 75% of postmenopausal women experience hot flushes (10), a symptom of estrogen withdrawal. Flushes also occur in young women after ovariectomy and are treated effectively by estrogen replacement (9,10). Flushes are characterized by peripheral vasodilatation, perspiration, and an intense sensation of heat (11,12). Although these are physiological mechanisms that normally reduce body temperature, the core temperature paradoxically is normal at the onset of a flush. Because heat loss mechanisms are activated in the presence of normal core temperature, flushing is considered a disorder of central (hypothalamic) thermoregulation (10). A second
line of evidence that the flushes originate within the hypothalamus is the finding that each flush episode coincides with a pulse of LH secretion into the systemic circulation (13,14).

The starting point of the present series of investigations was the seminal report by Sheehan and Kovács on neuronal hypertrophy in the infundibular (arcuate) nucleus of postmenopausal women (15). The phenomenon of postmenopausal neuronal hypertrophy was intriguing because of its association with estrogen withdrawal and the location of the neurons in the putative control center for reproduction (16). The enlargement of neurons more importantly did not appear to be secondary to a degenerative event. On the contrary, it was accompanied by morphologic signs of increased activity, such as enlarged nuclei and nucleoli, and increased Nissl substance (rough endoplasmic reticulum) (15,17).

Postmenopausal Neuronal Hypertrophy Occurs in a Subpopulation of Neurons Expressing Estrogen Receptor Gene Transcripts

Because the initial observations of neuronal hypertrophy were qualitative, our first task was to confirm and quantify these changes (17). Formalin-fixed, paraffin-embedded, cresyl violet stained sections were prepared from the hypothalami of pre- and postmenopausal women. An image-combining computer microscope was used to digitize neuronal profiles (18). This study clearly demonstrated that neurons in the infundibular nucleus of postmenopausal women are hypertrophied. We next hypothesized that the hypertrophy was due to the removal of the inhibitory feedback of ovarian steroids, analogous to the enlargement of pituitary gonadotrophs that occurs after castration in laboratory animals (19). We reasoned that if the cellular changes were secondary to alterations in levels of estrogen, then the hypertrophied cells would express the gene for the estrogen receptor. This was indeed the case (17). It is interesting to note that the hypertrophied neurons did not express gonadotropin releasing hormone (GnRH) mRNA (Fig. 3.1), a finding that was consistent with previous studies showing that the estrogen receptor and GnRH are localized within different subpopulations of hypothalamic neurons (20).

Neuronal Hypertrophy Also Occurs in the Infundibular Nucleus of Older Men

In contrast to the complete loss of ovarian steroids in older women (2), the reduction of gonadal steroid levels in older men is mild (21). Based on the modest reduction in testosterone, we predicted no change in the infundibular nucleus of older men, or that hypertrophy, if present, would be small in