An historical step in our understanding of hypothalamic oestrogen feedback

In 1957, Béla Flerkó and János Szentágothai implanted ovarian and liver tissue autografts into two distinct hypothalamic regions or the adenohypophysis of female rats. The tiny pieces of liver were absorbed. By contrast, the ovary implants survived and continued to release oestrogens. Furthermore, if the ovarian tissue was implanted below the hypothalamic paraventricular nucleus, the weight of the uterus decreased and the oestrous cycle of most animals was arrested in dioestrus. Both of these consequences, attributed to reduced peripheral oestrogen signalling, were absent in rats that had the ovarian implants in either the mammillary region or the adenohypophysis. Flerkó and Szentágothai interpreted their results as evidence that the oestrogen released from the ovarian grafts, which could not inhibit gonadotrophic activity via direct effects on the adenohypophysis, acted on the nervous tissue of the hypothalamus to inhibit secretion of follicle stimulating hormone.

The basic conclusion of the authors that oestrogens act predominantly in the hypothalamus to inhibit the secretion of gonadotrophs, has remained valid since 1957. However, it should be recognized that the lesion and implantation techniques available at that time did not allow these investigators to precisely determine the hypothalamic site where negative feedback takes place and results of lesion experiments directed their attention to the anterior hypothalamus.

In retrospect, we might suspect that the oestrogen-sensing 'nervous tissue' could correspond to neurons of the mediobasal hypothalamus expressing oestrogen receptor (ER) α, which are now thought to convey most of the negative feedback to neurons synthesizing gonadotropin-releasing hormone (GnRH). In 1990, Naomi Rance and colleagues reported that the ERα-expressing neurons of this putative feedback site respond with robust hypertrophy to the absence of oestrogens after menopause. In a series of follow-up studies using in situ hybridization, it has also been determined that the hypertrophied neurons are peptidergic and express increased levels of neurokinin B, substance P and kisspeptin.

Today, ERα-expressing neurons of the mediobasal hypothalamus and the mechanisms of sex steroid feedback are still being investigated intensely in animal models. Particular attention is being paid to a cell group that co-expresses kisspeptin, neurokinin B and dynorphin in the arcuate nucleus of rodent and ruminant species. These ('KNDy') neurons seem to have critical roles in pubertal development, sex steroid feedback and regulation of the secretory pulses of luteinizing hormone.

The discovery of Flerkó and Szentágothai is viewed as a real milestone in reproductive neuroendocrinology and its importance can be appreciated more from a historical perspective. In 1957, these investigators were aware that oestrogens inhibit secretion of follicle stimulating hormone from the adenohypophysis. They already knew from the results of previous lesion studies by Flerkó and others that this inhibitory effect is reduced in rats with anterior hypothalamic lesions, supporting the emerging hypothesis that the hypothalamus somehow contributes to the stimulatory regulation of gonadal function. Geoffrey Harris put forward his revolutionary concept in 1955, suggesting that the brain controls the endocrine system (including gonadal functions) by releasing humoral factors that communicate with the adenohypophysis.

The study of Flerkó and Szentágothai was reported in an era when the theory of specific ERs had not been introduced yet. The existence of ERs in peripheral endocrine tissues gained wide acceptance only in the 1960s and studies of tritiated oestrogen binding by Stumpf determined the distribution of ERs in the hypothalamus more than a decade after Flerkó and Szentágothai's study raised the intriguing possibility that the negative feedback effect of oestrogens on gonadotrophic functions is mainly exerted in the hypothalamus. Isolation of GnRH in the two competing laboratories of Schally and Guillemin (laureates of the 1977 Nobel Prize in Physiology or Medicine) only took place in 1971. It was not until the early 1980s that GnRH-synthesizing neurons of the hypothalamus were first visualized with immunohistochemistry. The idea that GnRH neurons might not represent the direct target cells of oestrogen feedback was first addressed in 1983 by Shivers and colleagues from the Pfaff laboratory. Although GnRH neurons turned out much later to express a second ER isoform (ERβ), most experimental data from the past four decades redirected attention to ERα containing neurons of the mediobasal hypothalamus. This area is the putative major feedback site where the ovarian implants in Flerkó and

Szentágothai's study also exerted inhibition on the reproductive axis.

This article intends to pay tribute to an important piece of work by two pioneers in the field of reproductive neuroendocrinology. János Szentágothai, Béla Flerkó, Béla Mess and Béla Halász represent the golden generation of Hungarian neuroendocrinologists from the 1950s and 1960s. Their new ideas, novel experimental approaches and original observations, reported in an influential book in 1962, considerably shaped our understanding of the hypothalamic control of the anterior pituitary.

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Competing interests
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