

EDITORIAL

## **Hypothalamic Releasing And Inhibitory Hormones: Historical Background**

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The award of Nobel Prize in Physiology and Medicine in 1977 to Roger Guillemin and Andrew Schally, two neuroendocrinologists, for their research on hypothalamic releasing and inhibitory hormones signaled an increased appreciation of brain-endocrine interactions. The historical background of this may be dated to the first half of 20<sup>th</sup> century when Otto Loewi and Henry Dale demonstrated that chemical transmission of nervous impulse was effective at nerve endings in the autonomic and peripheral nervous systems for which they shared the 1936 Nobel Prize. The 1930's witnessed a wealth of original research on the anatomy and physiology of the hypothalamus and its relationship to the neurohypophysis. It was thought that nerve impulses from the supraoptic and paraventricular nuclei controlled the secretion of neurohypophysial hormones vasopressin and oxytocin from gland cells in the posterior pituitary. Ernst and Berta Scharrer (1940) summarized their histological evidence that hypothalamic nerve cells, especially magnocellular components of the supraoptic and paraventricular nuclei were themselves secretory, and they suggested that hormones might be produced in such cells. The neurosecretion hypothesis received a lift when Bargmann and his students applied the Gomori chromalum hematoxylin stain (developed for pancreas study) to the brain and found the whole supraoptic-and paraventricular neurohypophysial system differentially stained. The octapeptide structures of oxytocin and vasopressin were established by du Vigneaud, another achievement recognized by the award of Nobel Prize in 1955.

The 1930's and 1940's were also a time for speculation that secretion of the newly described anterior pituitary trophic hormones might be controlled by humoral mediators from the hypothalamus. Evidence for hypothalamic control of anterior pituitary has come primarily from studies employing hypothalamic lesions or stimulation. In the mid-1930's it was shown that hypothalamic stimulation could induce ovulation in the rabbit whereas similar stimulation delivered to the anterior lobe was ineffective, indicating that the anterior lobe itself was not electrically excitable. Meanwhile, in England Green and Harris in England established the neurovascular concept by demonstrating the pituitary portal system in all classes of vertebrates, by observing the downward direction of blood flow in the living frog and later in the rat (1955).

With the acceptance of the neurovascular concept biochemists started their search for the identity of the humoral mediators or “releasing factors” as they came to be called. Since only very few amounts of these substances are present in hypothalamic tissue, this proved to be a herculean task. Consequently, isolation and determination of structure of these factors required the processing of hundreds of thousands and even millions of hypothalamic fragments. In the early 1960’s McCann and Harris independently demonstrated the existence of a specific gonadotropin releasing factor. The first releasing factor to be characterized was thyrotropin-releasing factor (TRF), a tripeptide, almost simultaneously and independently by Guillemin’s and Schally’s laboratories in 1969 and subsequently its name was changed to TRH. The structure of LHRH, now called GnRH, as a decapeptide was first announced two years later in 1971 by Schally’s laboratory while Guillemin’s laboratory registered a first in 1973 in announcing the structure of somatostatin as a tetradecapeptide which, among other actions, inhibits the secretion of pituitary growth hormone. In recent years other releasing hormones CRH, GHRH, PIF/PRF and several other neural peptides including substance P, the endorphins and enkephalins have yielded structural analysis. If we were to single out the contributions of one scientist whose research laid a foundation for remarkable achievements of McCann, Schally and Guillemin and for establishing Neuroendocrinology as a speciality it would have to be the inspired work of Geoffrey Harris (1955).