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# Discovery of Hypothalamic Hormones Controlling Pituitary Function.

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A means by which the brain could control the anterior pituitary gland was discovered by B. A. Houssay *et al*. (1933) (1). In the living toad they found that portal vessels drained blood from a primary capillary plexus in the median eminence (ME) down the pituitary stalk to the sinusoids in the anterior pituitary gland. Popa and Fielding (1) found these vessels in dead animals but believed that the blood flow was upward from the pituitary to the median eminence, a conclusion also reached in the living rabbit by G. W. Harris (1). Later with Green (1947) (1), he found that the flow was downward in the living rat. Since the blood pressure in the portal vessels is very low, it is likely that, depending on the conditions, flow can be either upward or downward. Additionally, the short portal vessels carry blood from the neural lobe across the intermediate lobe to the anterior lobe, thus delivering neural lobe hormones directly in high concentrations to the anterior lobe of the gland. This fact has been largely neglected (1).

We hypothesized that the anterior pituitary was controlled by a family of releasing factors, one for each pituitary hormone. The assay animal for these factors would be the rat with ME lesions. Histological examination of the brains of these rats indicated that the supraopticohypophysial tract had been interrupted in the ME, which was itself destroyed. Testing 48 h after lesions yielded a sensitive preparation. Indeed, if these rats had water intake of 100 ml or more 24 h after lesions, they were much to vasopressin but did not respond to non specific stimuli. We used these rats to demonstrate the CRF activity of synthetic lysine vasopressin given to us by Vigneaud (2, 3). He had just received the Nobel Prize for synthesizing this plus oxytocin.

Using this assay, we demonstrated CRH activity of rat and sheep stalk median eminence (SME) extracts. These were contaminated with ACTH and vasopressin and we quantitated their ascorbic acid depleting activity in our assay animals; roughly 80% of the activity was due to CRF (1959) (4). Royce and Sayers obtained similar results.

Our CRF was purified and separated on Sephadex G-25 followed by CMC chromatography (5, 6) from other releasing and inhibiting factors (1959-65). Because it was a much larger peptide (40 aa) than the other releasing factors, it defied structural characterization for many years. As late as the late 60's, the President of the American Endocrine Society drew a diagram of the hypophysial-adrenal axis leaving out the hypothalamus and CRF. Later we found that vasopressin potentiates the action of CRF on the pituitary (7).

Evidence that oxytocin might be a prolactin releasing factor was provided by Benson and Foley (1959). We confirmed their finding that oxytocin delayed the histological involution of mammary glands of rats from which the litter had been removed. Much later we obtained evidence for a physiological role of oxytocin in control of prolactin secretion (8).

Reflection made it seem odd that oxytocin, one of the three most abundant peptides in the body, the others being vasopressin and atrial natriuretic peptide, would have so little

function. As I was flying down to Rio de Janeiro, this obvious idea occurred to me. Furthermore, I guessed that it was involved in cardiovascular system function. When I arrived to the office of Jose Antunes Rodrigues, one of my long term collaborators, his assistant jumped at the idea and low and behold oxytocin has a physiologically significant role in physiology of the cardiovascular system to decrease rate and force of contraction of the heart and to dilate blood vessels (1997) (9). It is present in the heart and blood vessels and plays a role in development of the circulation. Oxytocin can convert stem cells into a sheet of synchronously beating cardiomyocytes (2002) (10). These studies complemented our studies of the role of ANP in the cardiovascular system and the body fluid homeostasis (1997) (11).

I felt that there should be both an FSHRF and a LHRH to control secretion of FSH and LH, respectively from the anterior pituitary. What we needed was an assay animal. Since the gonads are steroid-secreting glands like the adrenal, I hypothesized that LH might cause a depletion of ascorbic acid from the testis or from the corpus luteum obtained from pseudopregnant rats. I found little if any effect. That year (1958), the Federation Meeting was held in Philadelphia a stone's throw from my office. Amazingly, Al Parlow presented the assay for LH in young pregnant mares' serum (PMS) and human chorionic growth hormone (HCG) - injected female rats. I was amazed and immediately set out to verify his results. I also injected an 0.1 N HCl extract of rat stalk median eminences, the exact method used to extract CRF.

There was a dose-related effect of SME extract to deplete ovarian ascorbic acid and similar extracts from cerebral cortex had no effect. There was no effect of epinephrine, norepinephrine, serotonin or substance P.

I was going to the International Congress of Physiology in Buenos Aires in 1959 and had planned to give the results. Instead, after meeting Houssay and Leloir, the first a Nobel Laureate, and the second as stated by Houssay to become one, I met Samuel Taleisnik (director of the Institute in Cordoba), who was to join me in Philadelphia on the recommendation of Houssay. We took the night train to Cordoba. I asked him if he could do hypophysectomy in baby rats. He said he could. I showed him the data and told him that he'd being doing hypophysectomy in Philadelpia. He came and was on 9 papers in 1 year. We ruled out LH as a factor in the ascorbic acid depletion and published the first paper on LH-RF (12). I asked Taleisnik to stay and he said he couldn't because he was director of the Institute. After he left I showed that if you inject hypothalamic extract iv into ovariectomized, estrogen primed rats, blood LH increases. Also, LH-RF was a peptide based on enzymatic degradation studies.

At this time (1963), Masao Igarashi came from Japan. He brought with him a new more sensitive assay for FSH, the mouse uterine weight augmentation assay. The Steelman-Pohley assay was too insensitive for our studies. I told him that after a few improvements, his assay would be suitable and we would discover the FSH-RF. He presented the discovery of FSH-RF at the Endocrine Meeting in Atlantic City in 1963 and we published in full shortly after in 1964 (13). I had no experience and had no luck trying to recruit peptide chemists. Gel filtration on Shephadex G-25 appeared to be an ideal technique to separate small peptides. Therefore, I set up a small column of Shephadex G-25 and collected the fractions over night in the cold room. The peaks of FSH-RF and LHRH overlapped completely.

Fortunately, Anand Dhariwal arrived at this point. He set up a tall skinny Shephadex G-25 column. There was a clear separation of the FSH-RF eluting just prior to the LHRH

(1965). Schally confirmed these results using the FSH assay, shown to him on the way back to Japan by Igarashi. Now, Schally doesn't quote his own work which is doing severe damage to this field! Not only did we separate FSH-RF from LHRH but also from other releasing factors (5, 14).

We believe FSH-RF is lamprey GnRH III. Antibodies against it block the action of FSH-RF. It is localized to the dorsomedial preoptic area, an area that controls FSH release and not LH release (15). Mass spectroscopy of purified FSH-releasing hypothalamic extracts reveals a peptide with its molecular weight (umpublished data). Biotynilated L-GnRH III binds selectively to FSH gonadotropes, whereas biotynilated LHRH binds selectively to LH gonadotropes (15). FSH-RF mediates separate pulses of FSH (15).

It occurred to me that since mating behavior occurred in the rat shortly after LH was released to induce ovulation, that LHRH might induce mating behavior. I had no experience with mating studies. Therefore I hired Bob Moss, an electrophysiologist who obtained his PhD for sex behavior studies in rats. I told him my idea and said that when the structure of LHRH broke we would test it for mating behavior. It wasn't long until the structure was elucidated in Schally's laboratory by Matsuo. I called Schally and asked if we could have some synthetic LHRH. He said it already was being provided to people in 40 labs around the world. Fortunately, we got it quite soon without his help. I gave some to Moss and asked him to try it. Several months went by. Finally I called him in. He said he was sure it wouldn't work, so he hadn't tried it. I said I think it will work, try a high dose in ovariectomized-estradiol-primed rats. If it doesn't work you'll be finished with it, but if it works you'll be working with it for the rest of your life. It worked like a charm (16) and he worked on it until his premature death. **(Fig.1**)

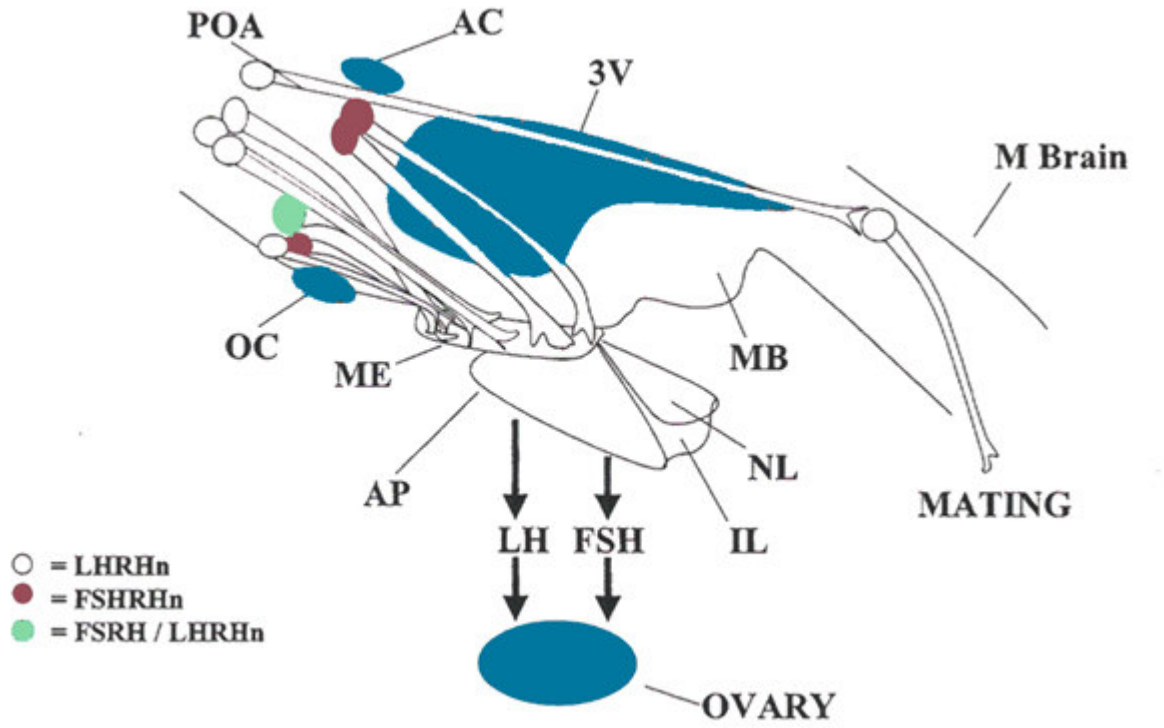


***Fig. 1.*** *Parasuggital section of preoptic and hypothalamic region of the rat brain illustrating the distribution of FSHRH and LHRH neurons. Abbreviations: POA = preoptic area, AC = anterior commissure, OC = optic chiasm, 3V = third ventricle, ME = median eminence, MB = mammilliary body, M Brain = midbrain, AP = anterior pituitary, IL = intermediate lobe, NL = neuronal lobe.*

*LHRH neurons arise in the medial preoptic area (MPOA) and project to the mid and caudal ME to release LHRH into the portal vessels for stimulation predominantly of LH and to a lesser extent of FSH.*

*FSH-RH neurons arise also in the MPOA slightly rostral to the LHRH neurons and project to the rostral ME. They release FSH-RH into the portal vessels to stimulate predominantely FSH and to a lesser extent LH. In the ventral MPOA, there are some neurons that contain both, FSH-RHand LHRH. The axons of another population of LHRH neurons descend to the midbrain central grey. The perikarya of all these neurons is activated by NO and cGMP. This last population mediates sex behaviour.*

We had earlier studied the effect of cAMP on hypothalamic pituitary function and since cGMP had no known functions and was a major cyclic nucleotide, we wondered if cGMP might have a role to play. Indeed, we found that cGMP mediated the action of GnRH's on the pituitary (17, 18). Now we know that NO stimulates gonadotropin release by cGMP (15). (**Fig. 2**)

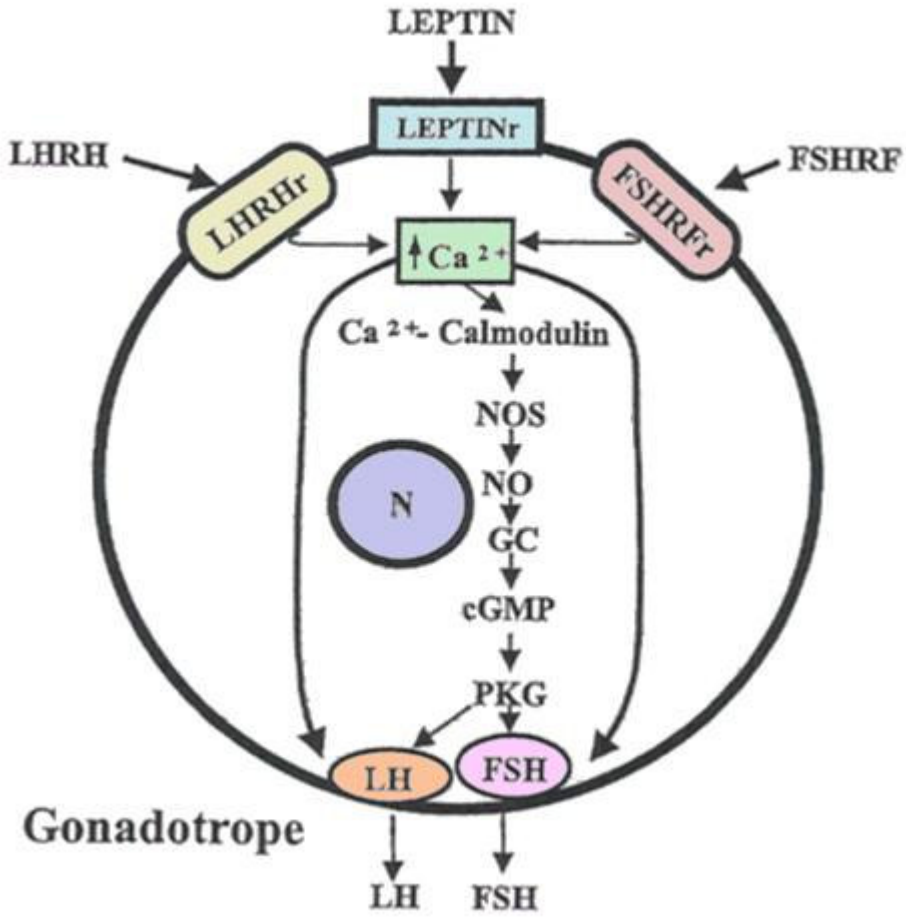


***Fig. 2.*** *Schematic diagram illustrating the mechanism of the gonadotropin-releasing action of FSHRH, LHRH and leptin, N = nucleus. The principal pathway is via NO, cGMP and PKG, but $Ca^{2+}$ may have an independent action.*

*FSH gonadotropes have FSHRH receptors in their cell surface. FSHRH interacts with FSHRH receptors to increase intracellular $Ca^{2+}$ that combines with calmodulin to activate NOS. The NO generated activates guanylyl cyclase which converts GTP to GMP that activates PKG leading to extrusion of FSH granules from the cell. LHRH acts analogously to release predominantly LH. If the cell expresses both receptors it will respond to both releasing factors. Leptin reaching the adenohypophysis acts on its own receptors to cause release of LH and to a lesser extent of FSH by the same pathway just described.*

Lad Krulich from Prague had been working with us for some years. We decided to see if our hypothalamic extracts would stimulate GH release from the pituitary. He would inject the stalk median eminence extract iv and then measure the depletion of GH from the

pituitary assayed by widening of the tibial epiphyseal plate of hypophysectomized rats. He quickly found a hypothalamic GH-RF and then switched to a better assay studying the effect of purified hypothalamic extracts on GH release from rat pituitaries *in vitro*. With Dhariwal he purified the GIF by gel filtration and CMC, separating it from the others releasing factors (19, 20).

Several years later Guillemin's group purified this peptide and synthesized it, renaming it somatostatin (1972). In the original version of this manuscript he didn't mention our work. The referees complained and it was changed to say that we had found it in crude extracts. That was a lie because crude extracts had a GH-releasing action. Somatostatin is a tetradecapeptide that has never been show to have growth inhibitory action. The name is a misnomer but still it is used.

We purified and separated all of these peptides that we worked on one from another. Gel filtration on Sephadex G-25 separated them more or less according to molecular weight. The larger the peptide, the earlier its elution. Therefore, the largest, CRF eluted followed by GRF, GIF, FSH-RF, LHRH and vasopressin (5). We discovered a peptidic PIF but did not persue this further since dopamine turned out to be a powerful PIF (15).

By cutting frozen section horizontally and frontally we localized the various RF's by bioassays in the preoptic and hypothalamic areas (21), results later confirmed by immunocytochemistry. Martini postulated that pituitary hormones would have a short loop negative feedback and that hypothalamic hormones would have an ultrashort negative feedback. We have found many examples of these actions (15), which probably act for all transmitters.

In the ovariectomized-estrogen-primed female rat the negative feedback of estrogen to decrease LHRH release is reversed and becomes positive to increase LHRH release by NO that stimulates LH release from the adenohypophysis but also acts in the brain stem to augment mating behavior by inducing lordosis. If also activates pelvic neurons which act by NO released in the corpora cavernosa penis to cause penile erection (15). This is but one example of the ubiquitous role of NO as a synaptic transmitter.

Acetyl choline, dopamine, NE, serotonin, glutamic acid, GABA and NO interact in complex ways to participate in hypothalamic control of releasing and inhibiting hormone release (15).

In 1966, we published our first study on neuroimmunomodulation which was a comparison of the effect of environmental and preoptic heating with that of fever induced by purified LPS that increased cortisol release in dogs (22). Twenty years later we determined the ability of proinflammatory cytokines to induce the pattern of pituitary hormone release during infection (23). With Valeria Rettori and Les Dees we showed with immunocytochemistry that there were some neurons containing IL-1 $\alpha$ among the dorsomedial preoptic temperature sensitive neurons and that they were dramatically induced by LPS (24). Ma Li Wong showed that IL-1 $\beta$mRNA could be induced in neurons in the paraventricular and arcuate nucleus by LPS (25).

With Omid Khoram and Jim Lipton we showed that $\alpha$MSH had an antipyretic effect on LPS-induced fever. Indeed $\alpha$ MSH is an anti-inflammatory cytokine (26).

With Tibor Wenger and Valeria Rettori we studied the hypothalamic action of $\delta$9-tetrahydrocannabinol, the active ingredient of marijuana (27). We believed that there must be an endogenous cannabinoid with appropriate receptors. We were pleased to see the

discovery of an endogenous ligand, anandamide (AEA) with two receptors, Cb1r and Cb2r. With Valeria Rettori and her group we have carried out extensive studies indicating that many drugs act by endocannabinoids activating Cb1r or Cb2r. For example the action of alcohol to suppress LHRH release can be blocked by a Cb1r blocker (28).

With Ramirez, we found that immature rats were excruciatingly sensitive to the negative feedback of gonadal steroids. After puberty the sensitivity declined several fold (29). Some time later Coleman discovered dwarfed obese sterile mice. The defect was in a single gene named obese (Ob). Only homozygous Ob-Ob mice showed the defects. Coleman parabiosed a thin mouse to an Ob-Ob mouse resulting in the fat mouse becoming thin. It was hypothesized that there was a hormonal defect in the fat mouse. People looked in vain for the hormone in the blood and in the urine. Nothing happened until Zhang and Friedmann by positional cloning obtained its structure, making possible the synthesis of leptin.

With Wen Yu we determined that leptin acted in the basal tuberal region to release LHRH by NO. It also acted on the anterior pituitary to stimulate LH and to a lesser extent FSH with the same potency as LHRH. With Claudio Mastronardi we discovered that leptin was present in adipocytes in large amounts and its secretion could be stimulated within 10 min. There was a circadian rhythm of plasma leptin with a peak at 1.30 AM and a nadir at 7.30 AM in man and rats. Finally, plasma leptin throughout the 24h paralleled that of $NO_2$-$NO_3$, suggesting that leptin stimulated NO. Indeed, leptin stimulated $NO_2$-$NO_3$ and TNF-$\alpha$ release from incubated epididymal fat pads (30). Finally, Julio Licinio demonstrated that Ob-Ob humans failed to go into puberty but that it could be induced by leptin, indicating that leptin is the major inducer of puberty (31).

In conclusion, we must be open to new ideas. One must take time to go over a problem considering all the possibilities for its solution. This is the way to get new ideas. The most important thing for progress is the new idea. Without it progress ceases.

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# XXII CONGRESO LATINOAMERICANO Y 1ER IBERO-AMERICANO DE CIENCIAS FISIOLÓGICAS

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**Buenos Aires, 4 al 7 de noviembre de 2006**

Este año tendrá lugar en Buenos Aires el XXII Congreso de la Asociación Latinoamericana de Ciencias Fisiológicas (ALACF). Esta reunión congregará a científicos originarios de América Latina trabajando en sus países de origen, en Estados Unidos, en Europa y alrededor del mundo. Fisiólogos no latinoamericanos de primer nivel son también regularmente invitados. Esta vez la Sociedad Española de Ciencias Fisiológicas se asocia al evento, dándole especial interés y relevancia.

El objetivo central del Congreso es dar, a los fisiólogos trabajando y viviendo en Latinoamérica, la posibilidad de entrar en contacto con referentes en su campo de trabajo. Esto será especialmente cierto esta vez para aquellos radicados en el Cono Sur del continente (Bolivia, Brasil, Chile, Paraguay, Uruguay y Argentina).

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