Some Clinical Applications for Gonadotropin Releasing Hormone Agonists

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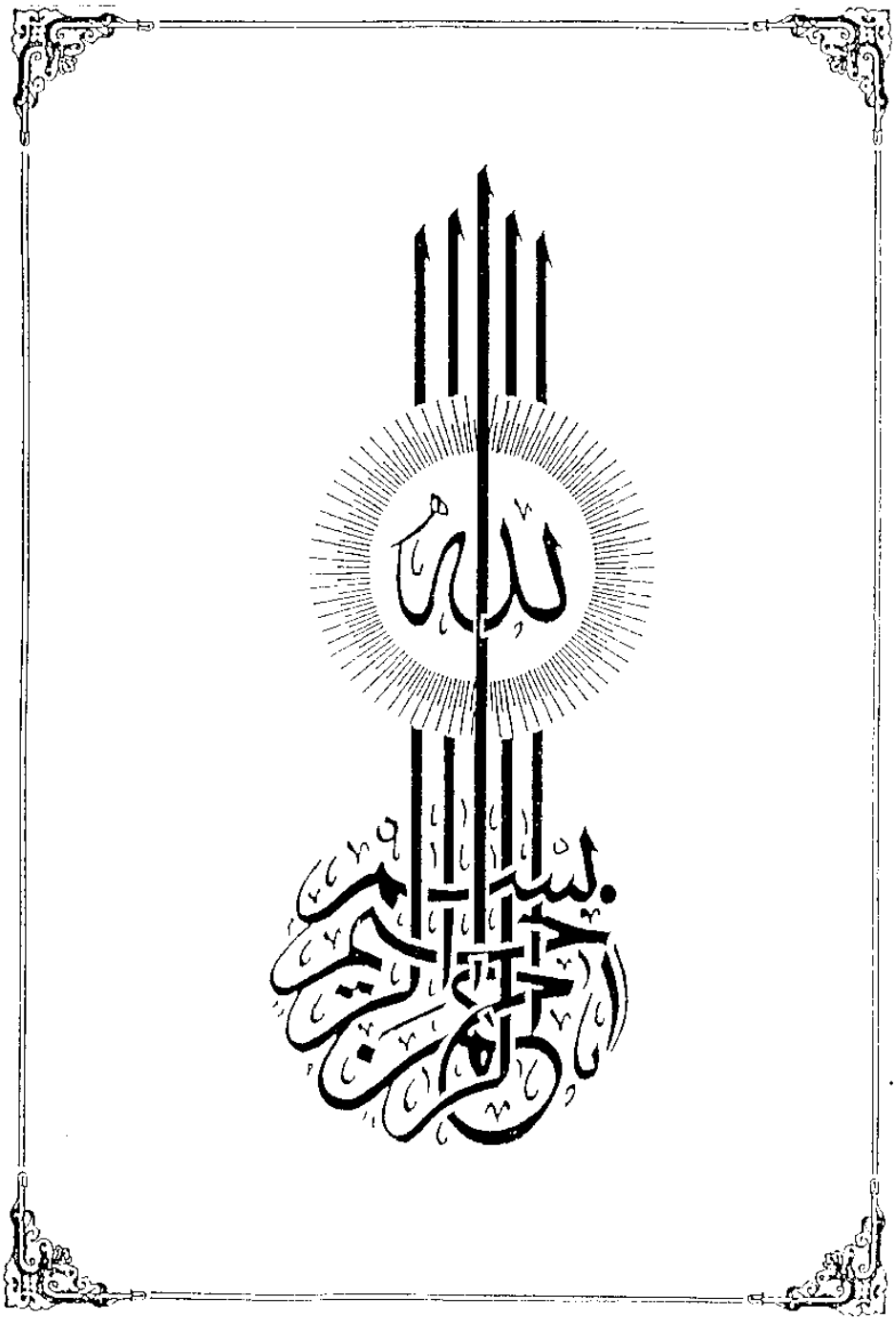

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List of Abbreviations

BPH	Benign Prostatic Hypertrophy
CAH	Congenital adrenal Hyperplasia
CRF	Conticotropin-Releasing Factor
DES	Diethylstilbesterol
DHT	Dihydrotestosterone
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GAP	GnRH-Associated Peptide
GH	Growth Hormone
GnRH	Gonadotropin Releasing Hormone
HCG	Human Chorionic Gonadotropin
HMG	Human Menopausal Gonadotropin
IV	Intravenous
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
MBC	Male Breast Cancer
MBH	Medial Basal Hypothalamus
m-RNA	messenger Ribonucleic Acid
NMDA	N-methyl-d-aspartate
OVLT	Organum Vasculosum of the Lamina Terminalis
POMC	Proopiomelanocortin
PRL	Prolactin
PSA	Prostatic Specific Antigen
Sm-C	Somatomedin-C
T	Testosterone
TPP	True Precocious Puberty

INTRODUCTION AND AIM OF THE WORK

Introduction

In early 1960s, considerable evidences accumulated, showing that, hypothalamic extracts possess the ability to release pituitary gonadotropins. Once the existence of such a neurohumoral factor was established, an extensive effort was directed to research work, which eventually led to the isolation, determination of molecular structure, and synthesis of luteinizing hormone-releasing hormone (LHRH) by *Schally et al.*, in 1971.

However, the name "LHRH" is now being challenged, as LHRH possesses both, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release activities. Therefore the name gonadotropin-releasing hormone (GnRH) was proposed and is currently used *(Wise et al., 1978)*.

Determination of the chemical structure of GnRH was followed subsequently by, the synthesis of many peptides which have nearly the same structure of GnRH, except for 1-2 amino-acid modifications. These structural modifications yielded compounds with potent agonistic activities (up to 100 times that of GnRH) *(Simon et al., 1990)*.

However, GnRH agonist administrations, after a short period of stimulating the gonadotrophs, paradoxically inhibits the secretion of LH, a phenomenon termed desensitization, with important clinical and therapeutic implications *(Jinnah and Conn, 1987)*.

Over the past 15 years, vast amount of literature has been accumulated, regarding the clinical use of GnRH or its agonists in many conditions such as true precocious puberty, endometriosis, polycystic ovarian disease, cancer prostate, metastatic male breast cancer, idiopathic hypogonadotropic hypogonadism, ... etc. *(Simon et al., 1990)*.

The aim of the present work is, to evaluate the information regarding the use of GnRH or its agonists in various clinical, diagnostic, and therapeutic applications in males and children.

HISTORICAL REVIEW

How GnRH Agonists were Discovered and Developed

The small area at the base of the skull that encompasses the hypothalamus and the pituitary gland has always attracted scientific curiosity. Early in medical history, physicians discovered that both structures are anatomically connected, but more importantly, they also postulated a functional relationship. Galenus, a physician practicing in ancient Rome, proposed the idea that impurities from the brain are drained through the pituitary into the nasopharynx, a concept that was to have remarkable longevity, 16 centuries. Drawing on this notion, the medieval pharmacopoeia included various sneezing powders "to purge the brain", a curious foreshadowing in view of the fact that at present, two major pharmaceutical corporations have developed gonadotropin-releasing hormone (GnRH) agonists to be administered by the nasal route *(Henzl and Lake Polan, 1993)*.

The galenic concept was first challenged in the 17th century by Schneider, a German scientist, and by Lower, an Oxfordian who served at the Royal Court of St James. They had the remarkable insight to propose that various substances are "distilled" from the pituitary into the circulation, adumbrating the modern concept of a gland with internal secretion *(Medvei, 1982)*.

Perhaps the first scientific investigation of the relationship between the central nervous system and reproductive function was conducted in 1913, when Stieve, a young professor at the Munich Medical School, put a caged fox in a chicken coop and observed that the hens immediately stopped laying eggs. This might have remained an amusing experiment of an eccentric scientist had not the two World Wars turned Europe and other parts of the world into a gigantic laboratory, that provided ample evidence that the nervous system exerts considerable control over the pituitary gland *(Medvei, 1982)*.

During World War I, nutritional deprivation was suspected to be the cause of wartime amenorrhea. After World War II, in 1947, *Bass*, a Prague gynecologist and himself a concentration camp prisoner, identified psychogenic factors as the primary cause of wartime amenorrhea by meticulous questioning of about 900 survivors. Other exhaustive documentation brought evidence that, psychogenic stress (fear, anxiety, danger) in humans is implicated in diverse reproductive symptoms ranging from paracyclic ovulation and sudden uterine bleeding to involution of ovarian follicles and testicular atrophy *(Stieve, 1952)*.

The World War II experience included an observation that some 30% of the United States aviator cadets were flunking out of the training courses and no one knew why *(Hoagland, 1975)*. To solve this mystery, researchers initiated studies to measure the adrenocortical response of aviators under conditions of danger and tension. The results indicated that such stresses enhanced adrenocortical output and "those men best able to resist fatigue in general called least on their adrenals when stressed." This research was stimulated by experimental work on the importance of the adrenal cortex in meeting stress and suggested that psychogenic processes, *e.g.*, experiencing danger, affect the function of the adrenal cortex *(Hoagland, 1975)*.

The chain of discoveries of the concrete pathways and substances by which the nervous system affects the pituitary gland began in the laboratories of scientists in the United States, Canada, England, Sweden, Hungary, and Czechoslovakia. The credit, however, for presupposing a functional relationship between the hypothalamus and glands with internal secretion should be given to the Viennese physician *Aschner* who, in 1912, described ovarian atrophy in dogs after creating an "experimental brain tumor" by injecting a small amount of paraffin into the "regio sub-thalamica." *Aschner* postulated that certain endocrinopathies originate in the hypothalamus. As we know, modern diagnostic imaging techniques have been able to detect hypothalamic and pituitary

neoplasms, in gonadal hormonal disturbances previously thought to be mostly functional.

The concept that the pituitary gland is regulated by the hypothalamus was formulated as early as 1933 *(Hinsey and Markee, 1933)*. Most of the subsequent research was devoted to the relationship between the hypothalamus and the gonadotropic pituitary function with sophisticated animal experiments involving transplantation of the pituitary into various parts of the brain, reimplantation of the anterior pituitary into the emptied sella, stereotactic lesions, electrical stimulation, stalk resection, and ultimately extracts from tons of animal hypothalami *(Everett, 1988)*. Central to the identification of the hypophysiotropic hormones, was the work of Harris -another great Oxfordian- showing that, in portal capillaries connecting the hypothalamus with the anterior pituitary, the blood flow is directed from the hypothalamus to the pituitary. Harris further proved that, nerve fibers of the hypothalamic nuclei liberate substances into the capillaries of this portal system and that these neurohumors, having been transported to the various trophic cells of the anterior pituitary, regulate their function. This discovery inspired a number of scientists to work with hypothalamic extracts and proceed with their purification *(Henzl and Lake-Polan, 1993)*.

However, there were two names who were repeatedly encountered: *Schally and Guillemin*. Initially both scientists--*Schally* in Montreal and *Guillemin* in Houston--not knowing of each other, became involved with the identification of the corticotropin-releasing factor (CRF) *(Saffran and Schally, 1955)*. In the mid-1950s, they succeeded in producing biologically active hypothalamic extracts, but CRF itself eluded attempts at purification and chemical definition for more than 25 years after the quest began *(Vale et al., 1981)*.

Scientists therefore, turned their attention toward other hypothalamic-releasing hormones. Thyrotropin-releasing factor (TRF) was extracted from the hypothalamus in crude form by *Schreiber's group* in Prague, Czechoslovakia, in 1961 and chemically defined as a tripeptide by

Schally et al., in 1972 and *Guillemin* in 1975. *Guillemin's and Schally's* greatest discovery, however, was GnRH: In 1971, they both independently achieved isolation, structural definition, and synthesis of this hormone and were awarded the Nobel Prize in 1977 *(Medvei, 1982)*.

Because native GnRH has a half-life of only about 5 minutes, efforts were made to create more active analogues, and soon numerous compounds were synthesized with a biologic potency of up to 200 to 300 times higher than that of native GnRH and with half-lives of up to 4 hours *(Kiesel et al., 1989)*.

Exploration of the role of GnRH in reproductive processes has led to new, unpredicted insights into the mechanisms of central nervous system control of gonadal function in primates. This was mainly due to elegant and insightful experiments of *Knobil* and his school of followers, first in Pittsburgh, Pennsylvania, and later in Houston, Texas *(Knobil and Hotckiss, 1988)*.

The resulting Knobil paradigm demonstrated the importance of the pulsatile mode of GnRH secretion and postulated a hypothalamic pulse generator of GnRH that is indispensable for initiation and maintenance of normal function of the pituitary-gonadal axis *(Grumbach and Kaplan, 1990)*. Meanwhile, research with GnRH analogues took an unexpected turn: It was found that during long-term administration instead of stimulating, gonadal function, these compounds paradoxically inhibited pituitary gonadotropins and consequently suppressed both ovarian and testicular function *(Humphrey et al., 1977)*.

The discovery of this paradoxical effect had far-reaching clinical implications. Although the therapeutic utility of the stimulatory characteristics of GnRH is limited to certain hypogonadal syndromes, the inhibitory effects of GnRH analogues are useful in conditions that benefit from suppression of gonadal hormones, and they are numerous. In the United States, GnRH agonists were approved for the treatment of prostatic carcinoma in 1984 (leuprolide injectable), for management of endometriosis in 1989 (nafarelin intranasal), and for precocious puberty in