

PROLACTIN HORMONE

IN

FEMALE FERTILITY AND INFERTILITY

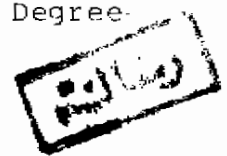


THESIS

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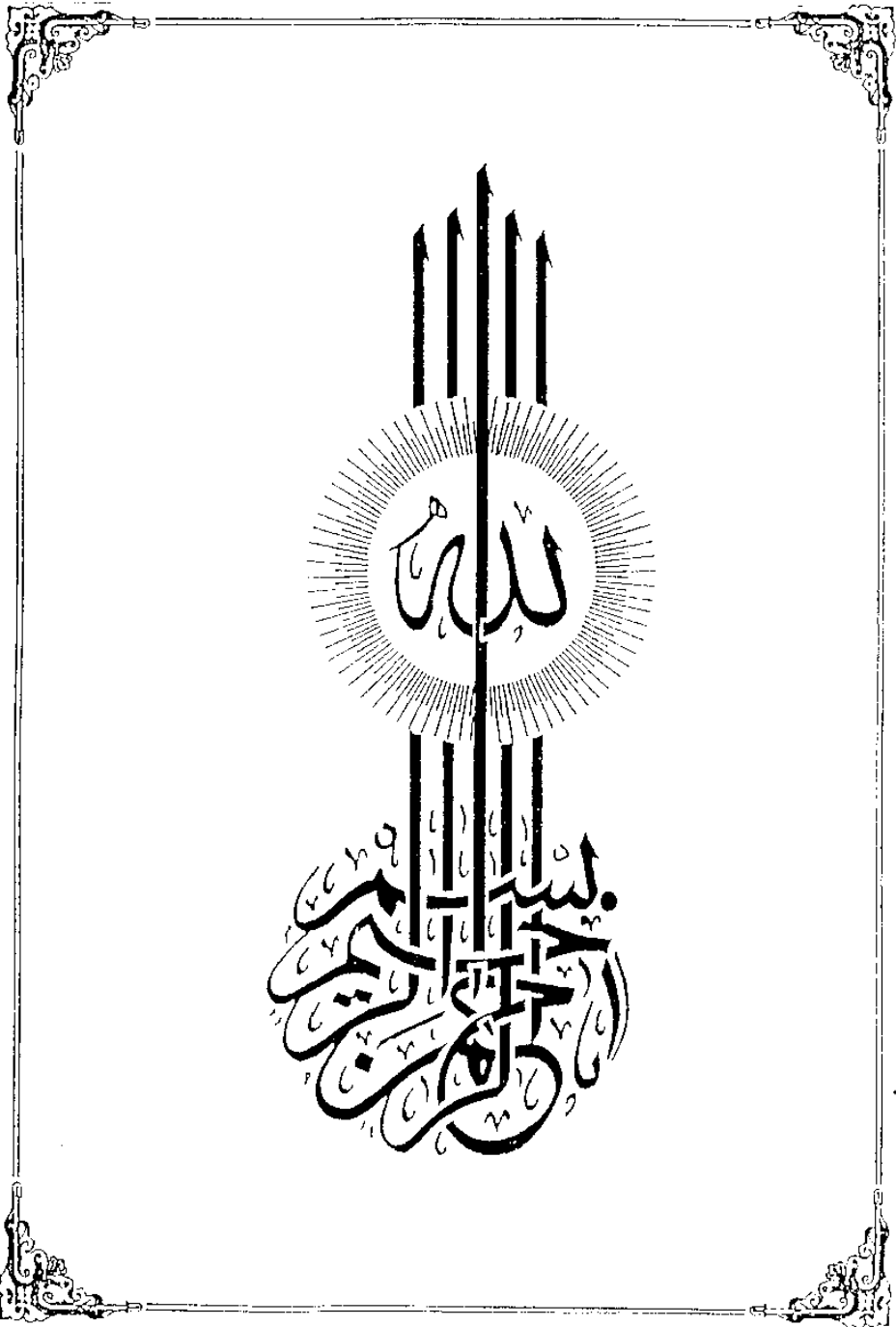
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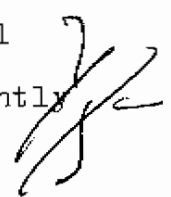


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INTRODUCTION

The knowledge that prolactin plays an essential role in the reproductive mechanism of women has recently led to a better understanding of female infertility. 

It has been known for some years that the regulation of the ovulatory cycle in women depends not only on proper LH and FSH secretion but also on the normal secretion of prolactin.] Whereas normal serum prolactin concentrations appear to be essential for the function of the corpus luteum in human beings, hyperprolactinaemia causes anovulatory cycles or amenorrhoea. Hyperprolactinaemia is found in 15 to 25% of patients with secondary amenorrhoea and therefore represents an important infertility factor.

Prolactin secretion in man in different physiological states and pathological conditions was rapidly characterized after the development of the radioimmunoassay for human prolactin by Hwang, Guyda and Friesen in 1971.

This thesis is a concise account of prolactin in female reproduction.

RECOGNITION AND IDENTIFICATION OF PROLACTIN HORMONE

Prolactin, a denomination of an unknown hormone introduced by Riddle and coworkers in 1933, owes this name to its stimulating effect on milk secretion.

As in the case of other pituitary hormones prolactin was defined by its biological characters, such as mammatrophic and luteotrophic effects in mammals, prior to its isolation as a molecule.

In the human, it was widely assumed for a long time that growth hormone fulfilled both growth promoting and prolactin activities.

Failure to isolate from human pituitaries collected postmortem a prolactin definitely distinct from growth hormone, and the intrinsic lactogenic activity of highly purified human growth hormone preparations supported the controversy as to the existence of a human pituitary prolactin.

On the contrary, many physiopathological and experimental data favour its existence. The earliest evidence came from the work of Pasteels (1962) who found that in vitro cultured human adult and fetal pituitaries

secreted increasing amounts of a pigeon crop-sac stimulating material, whereas growth hormone secretion in the tissue culture medium declined with time,(15).

In 1971 it was agreed that prolactin exists in the human as an anterior pituitary hormone distinct from growth hormone following the demonstration of its in vitro biosynthesis (45).

Lactotrophic cells
with eosinophilic granules
- 4 -

PROLACTIN FORMATION

Prolactin is produced in lactotropic cells found in the lateral wing of the anterior pituitary gland (Fig.1), together with the cells that produce the growth hormone.

The lactotropic cells, which contain eosinophilic granules, can be distinguished from somatotropic cells by their affinity for erythrosin or carmosin stains.

The number of lactotropic cells is increased in fetal pituitaries and during pregnancy. This proliferation of lactotropic cells is the result of very high concentration of circulating estrogens in human pregnancy (131).

Prolactin is synthesized within the cisternae of the endoplasmic reticulum and packaged by the Golgi apparatus into small membrane bound progranules, which are used to form larger mature acidophilic secretory granules.

The contents of the cells are then secreted by exocytosis resulting from fusion of the membrane of the granules and that of the cell (64).

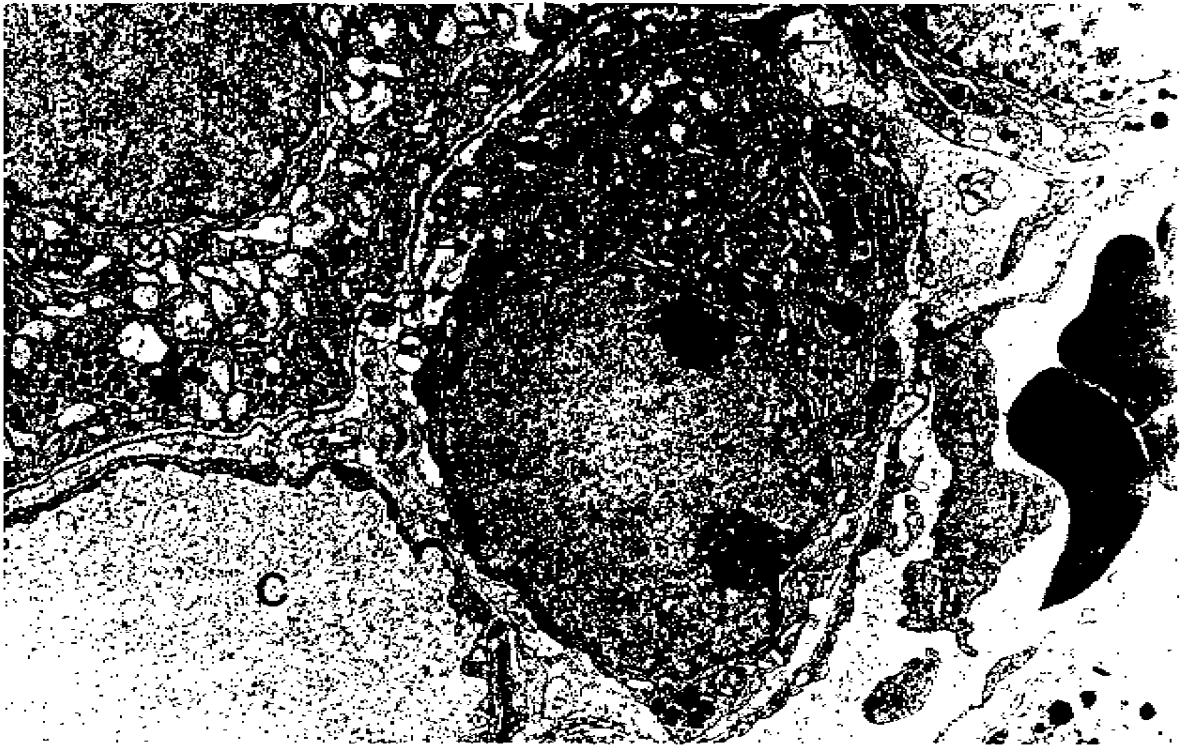


Fig. 1 Electron microscopy is used to study the secretion of an anterior pituitary hormone. In the middle of the micrograph can be seen a prolactin cell, which can be recognized by the irregularity of its secretory granules. There is a nucleus containing scattered chromatin and two nucleoli (nu), and also cytoplasm with abundant granular endoplasmic reticulum (ger) which is evidence of considerable synthesizing activity. There are also indications (arrows) of the contents of secretory granules being discharged by exocytosis into the perisinusoidal space. This secretion will find its way to the capillaries (C).
(Jeanine-Anne Heuson-Sticnon and André Danguy, Histology Laboratory, Faculty of Medicine, University of Brussels)

CHEMICAL STRUCTURE OF HUMAN PROLACTIN

The human prolactin molecule consists of 200 amino-acid residues, 3 disulfide bridges, and leucine as the NH_2 Terminal residue, (Fig.2).

There is a significant similarity in the amino-acids sequence of human placental lactogen (HPL), growth hormone (GH), and prolactin but GH and HPL differ by having only 2 disulfide bridges (76).

Prolactin, GH, and HPL may have evolved by genetic reduplication from a smaller common peptide; all are single-chain polypeptides without carbohydrate.

The prolactin molecule is very susceptible to inactivation by proteolytic enzymes present in the pituitary. It has a molecular weight of about 22,000, although the occurrence of prolactin of larger molecular size has been described in the serum of a patient with a pituitary tumour (101).

Prolactin from pituitary, serum and amniotic fluid was shown to be of the same chemical nature (10).

There is a remarkable homology between human and ovine prolactins, thus explaining their cross reactivity in radioimmunoassay.



Fig. 2

The linear amino acid sequence of human pituitary prolactin. Encircled residues, only, are identical with human growth hormone sequence. Modified from Shome & Parlow (1977).

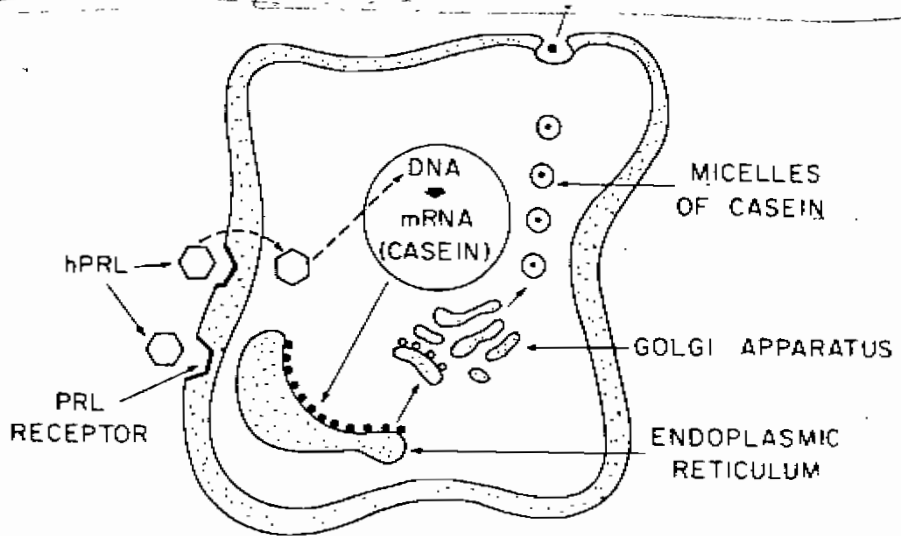
MODE OF ACTION OF PROLACTIN HORMONE

Prolactin interacts with the cell membrane receptor (S).

The altered state of the cell membrane is then translated into intraceullular signals to the nucleus, (Fig.3).

Altered intranuclear transcription is then coordinated to provide the ribosomal, transfer and messenger RNAS required for the synthesis of milk proteins and other mammary enzymes (119).

Fig.3 | Schematic representation of PRL-induced synthesis of casein in the puerperal breast.
After (Clin. Obst.& Gyneco.12:23,1980)



REGULATION AND MECHANISM OF SECRETION OF PROLACTIN

Prolactin is under the tonic inhibitory effect of prolactin-inhibiting factor (PIF), which is secreted from the hypothalamus. When it reaches the anterior pituitary, it acts on the lactotropes by suppressing them and it keeps the prolactin at a normal level. It is believed that there are two mechanisms in the hypothalamus that control the secretion of the hormone: One is a dopaminergic mechanism and the other is a serotonergic mechanism. It is believed that dopamine is the hypothalamic substance which inhibites the secretion of prolactin from the pituitary gland, (Fig.4). According to the work of Takahara and co-workers, dopamine is secreted into the portal circulation to reach the anterior pituitary and produce its effect directly on the lactotropes (113). /

The anterior pituitary is known to have dopamine-rgic or alpha-adrenergic receptors. L-dopa or dopamine could act at both the hypothalamic and pituitary levels. The anterior pituitary in vitro releases high levels of prolactin. Following incubation with catecholamines, there is suppression of prolactin secretion.

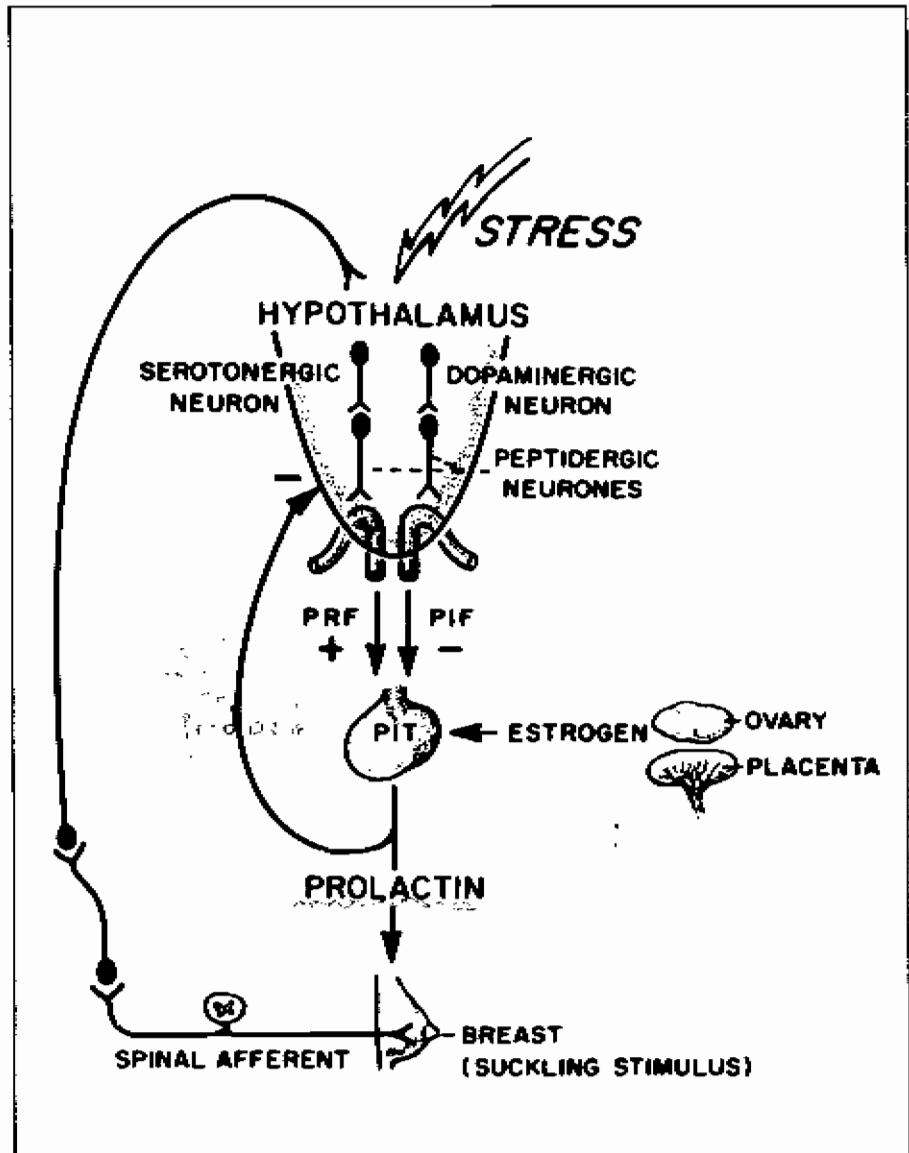


Fig.4

Hypothalamic control of prolactin secretion from the pituitary (PIT). The hypothalamus normally inhibits prolactin release by a prolactin-inhibiting factor (PIF), which appears to be dopamine. There is also evidence of the existence of hypothalamic prolactin-releasing factors. Neural inputs such as stress and suckling act upon the hypothalamus. There seems to be a short-loop feedback regulation of prolactin secretion. Oestrogen from the ovary and placenta regulate pituitary sensitivity to hypothalamic factors. From Martin et al. (1977), with permission.