ASSAY OF PROLACTIN LEVEL IN BLOOD IN CASES OF IRRITABLE BOWEL SYNDROME UNDER TREATMENT WITH SULPIRIDE

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF
MASTER DEGREE IN GENERAL MEDICINE

BY
SHERIF AHMED ISLAH MOHAMMED
M. B. B. Ch.

Supervised by

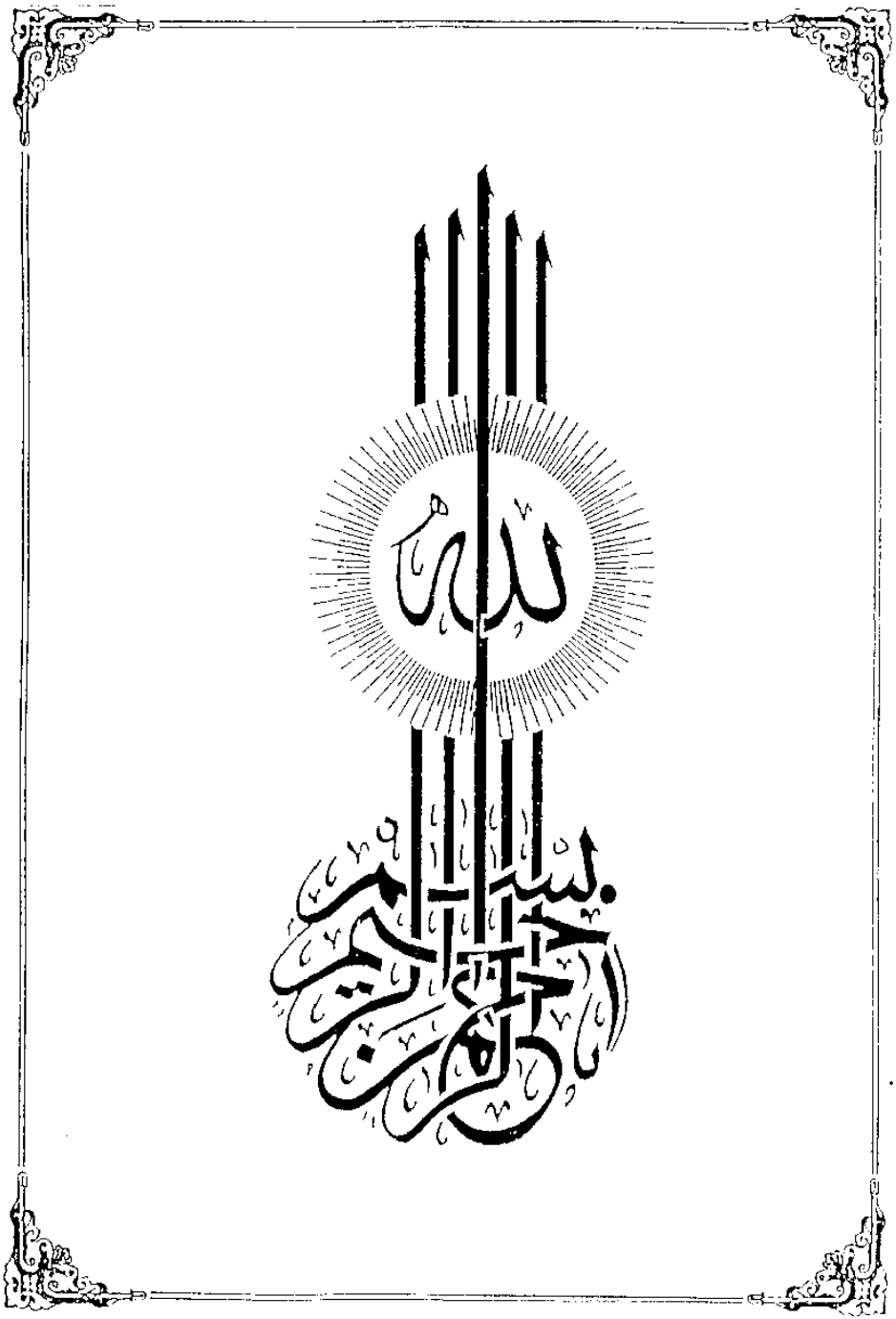
PROF. DR. MOHAMMED A. SALLAM
Prof.of Medicine
Ain Shams University

PROF. DR. YEHIA MAHRAN
Prof. of Medicine
Ain Shams University

DR.SOHEIR M.GAMAL EL-DIN
Assist. Prof.of Med.
Ain Shams University

DR.MOHSEN MAHER
Lecturer of Medicine
Ain Shams University

1986



ACKNOWLEDGEMENT

****

I wish to express my gratitude and appreciation to Prof. Dr. Yehia Mahran and Prof. Dr. Mohammed A. Sallam who suggested and followed up this work, for their consistent supervision and valuable suggestion.

Sincere thanks are also due to Assist. Prof. Soheir Gamal El-Din for her useful advice and for the facilities given to this work.

I would like to offer a special gratitude to Dr. Mohsen Maher for his endless support and his keen follow up of this work.

I wish to express my appreciation for the kind help I received constantly from the " Scientific Office of Delagrange in Cairo ". To all the colleagues in the " Gastroenterology Department " and to all the laboratory staff of the " Endocrinology Department " in Ain Shams University Hospitals, I wish to give my gratitude personally for each.

Last but not least, I would like to express my obligation to all the patients who participated in this work for showing utmost cooperation.

To My Mother

My Father

and Hanan

CONTENTS

FOREWORD AND AIM

OF

THE WORK

F O R E W O R D

Irritable bowel syndrome is a common disorder characterized clinically by abdominal pain, irregular bowel habits, and the absence of detectable organic gastrointestinal abnormalities (Chaudhary N. et al.,1962).

This syndrome has many names, as nervous diarrhoea, functional diarrhoea, mucous colitis, spastic colon and colonic enterospasm. However, many patients do not have diarrhoea, colitis implies inflammation, and spasm is not always present; so, most of these terms are unsuitable. Since both the small bowel and the colon are involved (Drossman et al., 1977), so, " irritable bowel syndrome " seems to be the best description (Taylor I. et al., 1980).

The irritable bowel syndrome is caused by intestinal dysmotility, the cause of which is unknown, but emotions and irritative factors such as a refined diet, food-allergy, dysentery and laxative abuse are felt to be important.

The post prandial abdominal pain and bloating in these patients appear to be related to an increase in the colonic motility (Connell A. M. et al., 1968).

The presence of specific dopaminergic receptors in the G.I.T. with contrasting actions on different regions has been clearly shown, and dopamine was proved to increase the colonic motility (Lanfranchi G. A. et al., 1978).

Sulpiride, a benzamide derivative, selectively antagonises dopaminergic receptors within and outside the C.N.S., and it is widely used in Euroupe as an antipsychotic, antidepressant and antiemetic, especially in the treatment of somatic complaints in neurotic patients (Spano P. et al., 1979).

Sulpiride was successfully tried to inhibit the post prandial colonic motility in patients with irritable colon (Lanfranchi G.A. et al., 1983).

However, its administration induces a marked rise of the serum prolactin level (Mancini A.M. 1976), and the prolactin response is positively correlated to the prolactin base line value (Wiesel F.A. et al., 1982).

AIM OF THE WORK

To study the effect of administration of sulpiride on serum prolactin level in humans.

PHYSIOLOGY OF PROLACTIN

Prolactin hormone is one of the anterior pituitary hormones, secreted by cells called mammotrophs, that constitute a part of the chromophils of the pars distalis.

CHEMISTRY AND PITUITARY STORAGE : (Daughaday W.H.,1981)

Prolactin is a simple protein, slightly larger than growth hormone, consisting of 198 amino acids in a single peptide chain. There are 3 disulphide bridges in the molecule, one of which is at the amino end of the molecule.

The normal pituitary contains little prolactin, about 100 µg, but a significant increase in the content of prolactin occurs during pregnancy.

SERUM LEVEL OF PROLACTIN

Serum levels of prolactin are both age and sex dependent. The prolactin concentration in neonatal boys is very high, but declines and approaches the adult basal value by th sixth week of age; from this time till puberty, there is no significant difference in the concentration of prolactin at various ages in both sexes (Guyda H.J. et al., 1973).

The mean serum prolactin level of women is about 10 ng/ml with upper limits of normal of about 20 ng/ml. The mean serum concentration of men and prepubertal children is slightly lower. During the hours of sleep, there is a moderate progressive rise in prolactin concentration (Daughaday W.H. 1981). Also it appears that prolactin levels are consistently higher during the luteal phase than during the follicular phase of the menstrual cycle (Ross G.T. 1981).

Prolactin has a volume of distribution that approximates that of extracellular fluid. After exogenous administration or suppression of endogenous secretion, prolactin disappears from plasma rapidly. The disappearance curve is complex but the major portion of prolactin has a plasma half life of 20 - 30 minutes. Both liver and kidney are important sites of degradation (Daughaday W.H., 1981).

REGULATION OF PROLACTIN : (Rechlin S.,1981).

There are different factors that influence serum prolactin level in humans:

(1) FACTORS INCREASING SERUM PROLACTIN :

- Physiologic factors :
  1. Pregnancy
  2. Postpartum
     a) Non nursing mothers (days 1 - 7).
     b) Nursing mothers after suckling.
  3. Nipple stimulation (males and females)
  4. Sexual intercourse (some subjects)
  5. Stress
  6. Exercise
  7. Neonatal period (2-3 months).
  8. Sleep.

- Pharmacologic factors:
  1. T R H
  2. Psychotropic drugs
     a) Phenothiazines
     b) Reserpine
  3. Oral contraceptives
  4. Oestrogen therapy
  5. Alpha methyl dopa.

- Pathologic factors:
  1. Prolactin secreting pituitary tumours .
  2. Hypothalamic - pituitary disorders.
     a) Tumours(craniopharyngioma) - metastases
     b) Histiocytosis X
     c) Inflammation - sarcoidosis
     d) Functional ?
  3. Pituitary stalk section
  4. Hypothyroidism
  5. Renal failure
  6. Ectopic production by malignant tumours

(2) FACTORS DECREASING SERUM PROLACTIN :

- Physiologic : Water depletion
- Pharmacologic : 1. L-Dopa
  2. Apomorphine
  3. Bromocryptine
- Pathologic : Isolated pituitary prolactin deficiency.

All forms of external and internal stimuli that modify prolactin release converge on the tubero-hypophyseal neurons that in turn, regulate prolactin secretion from the anterior pituitary by secreting prolactin inhibiting factors $PIF_{(s)}$ and prolactin releasing factor(s) $PRF_{(s)}$.

PROLACTIN INHIBITING FACTOR(s) $PIF_{(s)}$:

- Dopamine is the most important PIF. It is the neurohormonal product of one set of neurons of the arcuate nucleus that terminates in the median eminence. Secreted into the hypophyseal portal blood, dopamine exerts a direct inhibitory control on pituitary lactotrope cells by way of cell membrane dopamine receptors.

- Gamma amino butyric acid (GABA), a constituent of hypothalamic extracts, is also an active PIF but its presence in portal vessel blood in appropriate concentrations has not as yet been established.

- Histidyl proline diketo piperazine may be the third PIF. It is a cyclic degradation product of thyrotropin releasing hormone (TRH) formed by incubation with hypothalamic tissues.

There may be additional $PIF_{(s)}$ as well, but the relative importance for each remains for future elucidation.

Noteworthy is that all of the known prolactin inhibitory functions of the hypothalamus, can be explained by dopamine alone, though not all the PIF activity of the hypothalamic extracts can be so explained.

PROLACTIN RELEASING FACTORS(s) $PRF_{(s)}$:

The best characterized one being thyrotropin releasing hormone (TRH), this substance releases prolactin from normal pituitaries and follows the same dose response pattern as for TSH release. Yet, TRH is probably not the only PRF. Hypothalamic extracts bring about prolactin release even when the TRH content has been inactivated or separated chromatographically. It is unlikely that TRH plays more than a modulatory role in prolactin regulation under normal circumstances.

Recently, Abe H. et al., (1985) found that vasoactive intestinal peptide (VIP) is another candidate for PRF. This peptide was originally isolated from porcine intestine, but is widely distributed in the mammalian central nervous system including the hypothalamus.