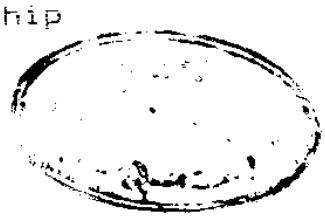
METABOLIC RESPONSES TO CHRONIC ADMINISTRATION OF SALINE

THESIS

Submitted In Partial Fulfilment

For The Degree Of Mastership

(PHYSIOLOGY)



By

MOHAMED HAMDY MANSY MOHAMED

Supervised By

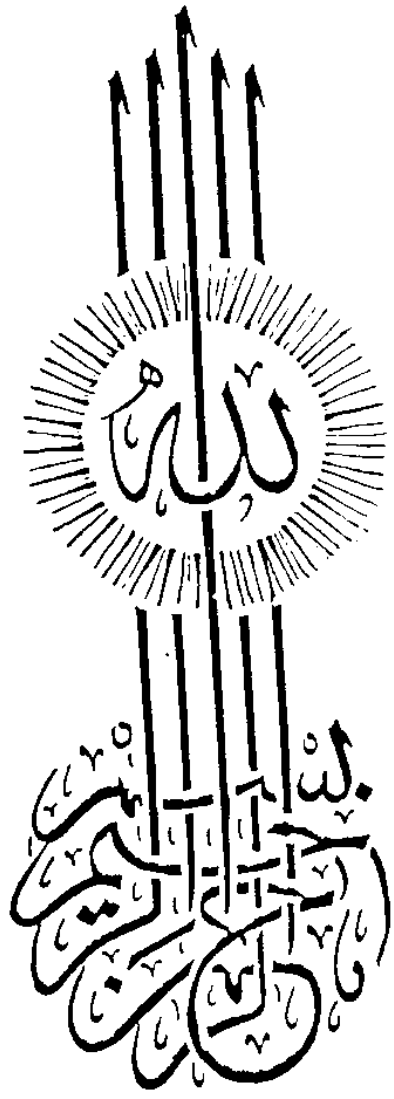
Dr. NABIL A.EL-DAMARAWY
Professor of Physiology
Faculty Of Medicine
Ain Shame University

Dr. MOHAMED RIFAAT A. RIFAAT
Ass.Professor of Physiology
Faculty of Medicine
Ain Shams University

Dr. HOSSAM EL-DIN A. AWAD
Lecturer of Physiology
Faculty of Medicine
Ain Shams University

Physiology Department
Faculty of Medicine
Ain Shams University

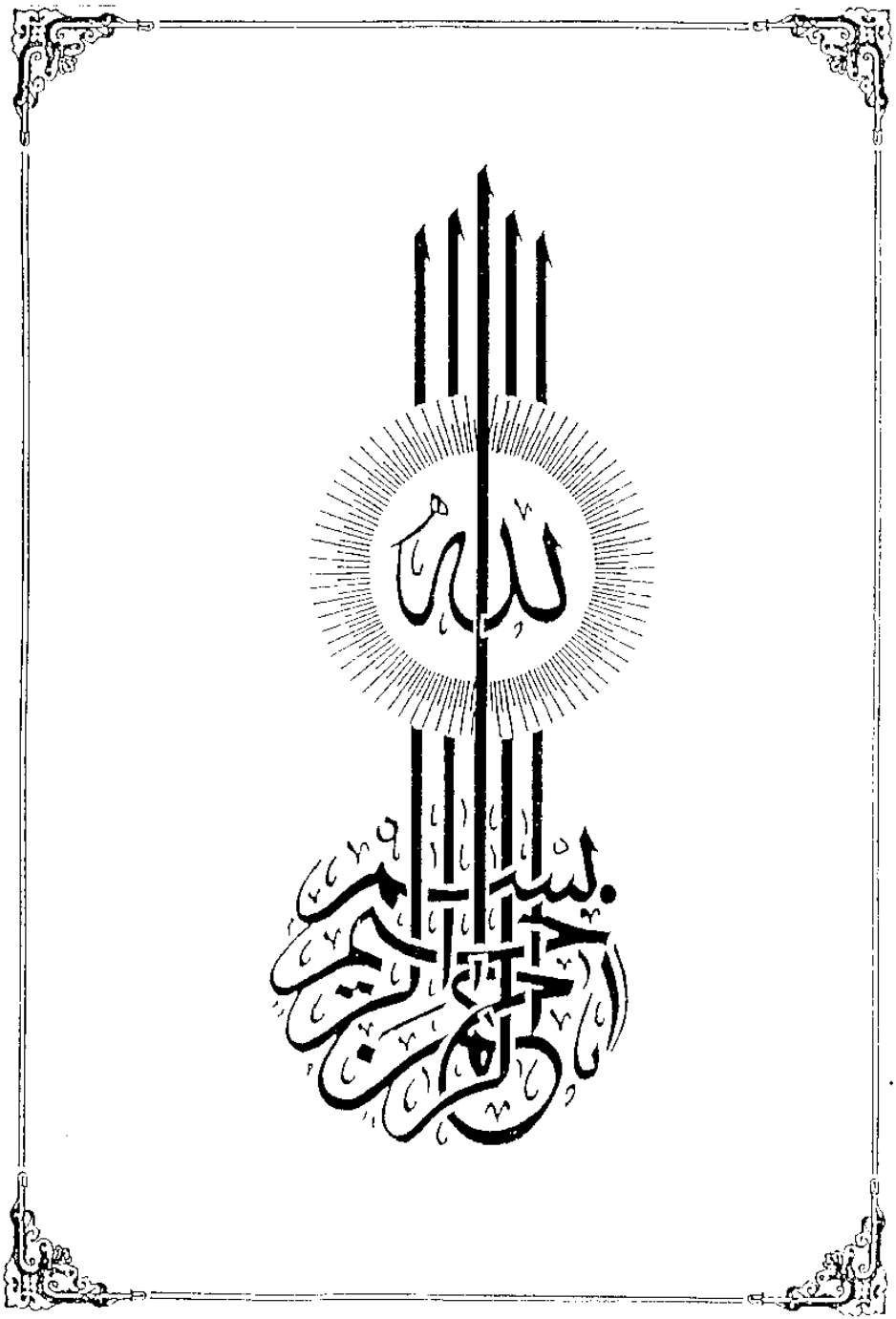
1991



وما أوتيتم من العلم إلا

قليلا

﴿ صدق الله العظيم ﴾



ACKNOWLEDGEMENT

I am deeply grateful to professor **MAHMOUD HANI AYOBE**, Head of physiology Department, for his help throughout the work. He allowed me to use the facilities of the cardiovascular research unit, physiology Department, and provided financial support throughout its funds.

I wish to express my deep thanks to professor **NABIL AHMED EL-DAMARAWY**, professor of physiology, for suggesting this study.

I am also profoundly grateful to Dr. **MOHAMED RIFAAT**, ass. professor of physiology, and to Dr. **HOSSAM AWAD**, lecturer of physiology, for their constant supervision and advice throughout this study. Without their help and support, this work could not have been possible.

Finally, I would also like to thank all members of the physiology Department for their support and encouragement.

CONTENTS

INTRODUCTION

INTRODUCTION

Although the relation between an ionic saline administration and its effect in elevating blood pressure is well established, yet there are only meagre reports in the literature concerning the metabolic responses to sodium chloride.

Recently, **Awad et. al., (1989),** demonstrated that short-term administration of isotonic saline in rats induced a hyperlipidemic state associated with hyperinsulinaemia. They ascribed these changes to peripheral resistance to insulin. However, the role of lipolytic hormones such as cortisol in this sodium chloride-induced hyperlipidemia has not been investigated and is worthy to study.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The question of a possible interrelationship between salt ingestion and carbohydrate metabolism was first aroused by **McQuarrie, et. al., (1936)** who reported that sodium chloride ingestion in a dose of one-two gm/kg b.w. for two to four days in man resulted in a decrease in fasting blood sugar level.

In our department **El-Gindi, et. al., (1982)** demonstrated a significant lowering of blood glucose level in some groups of dogs as a result of administration of saline. In a recent study, **Awad, et. al., (1989)** showed that repeated intraperitoneal injection of isotonic saline in a dose of 1 ml/kg.b.w. in rats for one week, resulted in a significant rise of plasma level of insulin, although the blood glucose was not significantly altered from the control group.

In vitro studies most of the investigations have been focused on the role of Na^+ on the B-cells of pancreas as reported by **Hales and Milner (1968)** who showed that both sodium and calcium must act at the B-cell membrane or enter the cell before insulin release can occur in response to a variety of stimuli. Moreover, **Lowe, et. al., (1976)**, showed the importance of Na^+ on the calcium dependent exocytotic release of insulin from the pancreatic B-cell suggesting that Na^+ could act as a physiological releaser of Ca^{++} from intracellular stores. Using tetrodotoxin, a specific inhibitor of sodium channels in

excitable membranes leads to a rapid block of insulin release, and also increases in sodium content have been proposed as an important component in the glucose stimulation of insulin release from the pancreatic B-cells as reported by **Donatsch, et.al., (1977). Wesslen and Hellman (1988)** demonstrated that increased extracellular sodium leads to release of Ca^{++} from intracellular pools, that act as a second messenger in exocytotic release processes for insulin.

More light was sheded on the effects of saline administration on lipid metabolism, much of this interest derives from the notion that chronic saline intake for four weeks resulted in no appreciable changes in serum cholesterol and triglycerides levels regardless of the sodium content of the diet and the subjects were not hyperlipidemic except for one man who showed moderate hypercholesterolaemia, as reported by **Kirkendall, et.al., (1976)**. On the other hand, **Hayek, et. al., (1983)** demonstrated that in vitro, chronic administration of saline in rats resulted in significant increase in serum cholesterol and triglycerides although the mechanism of action to account for these observed lipid abnormalities could not be ascertained, yet several possibilities were considered. The enhanced triglycerides formation may be due to inhibiting the conversion of fatty acids to ketone bodies in hepatocytes.

In support of this idea and in strict agreement with findings by [Greenbaum and McLean, 1953; Feigelson, et.al., 1961; Rudman, et.al., 1965; Zimmerman, et.al., 1973; Hotta, et.al., 1981 and Brindley 1981], who reported that hyperlipemia and fatty liver are the results of stress reactions mediated by the lipolytic hormones, catecholamines, growth hormone, ACTH and cortisol acting through increasing FFA-mobilization and the vasopressin released as a result of hyperosmolal state may also play a role in hyperlipemia either directly through its effect on adipose tissue or indirectly by stimulating the secretion of anterior pituitary hormones, however, **Hayek, et. al., (1983)** aroused a question that chronic excess sodium chloride intake, in the absence of hypernatremia, also disturbs lipid metabolism in humans or animals.

These biochemical changes in lipid metabolism occurred after administration of saline have been well documented by a recent study in our department conducted by **Awad, et.al., (1989)** who demonstrated hypercholesterolaemic and hypertriglyceridaemic effects in rats which were explained by a hepatic effect enhancing lipid synthesis. It is of interest to state that **Awad, et.al., (1989)** observed a significant rise in triglycerides and cholesterol in the control saline-treated rats in the study of **Turlapaty, et.al., (1980)** on vascular responsiveness and plasma lipids in diabetic rats, although they used a dose of 0.3-0.4 ml/rat w.i.p. for one week which is much less than that used by **Awad, et.al., (1989).**

A close association between saline administration and hormonal changes has been observed, the expansion of the extracellular fluid volume by i.v. infusion with isotonic saline causes the release of a humoral agent which inhibits sodium reabsorption in the proximal tubules augmenting sodium excretion which is neither by an increase in glomerular filtration rate nor by suppression of aldosterone secretion [De Wardener, et. al., 1961; Levinsky and Lalone 1963, and Rector, et.al., 1968]. Many investigators proved that these effects are mediated by the release of natriuretic hormone [De Wardener, et.al., 1961; Early and Friedler 1964; Morise, et.al., 1985 and Sagnella, et.al., 1985].

The information about increasing the osmotic pressure of plasma as determined the by measurement of cortisol by Decourt and Lahlou, (1986) who demonstrated that an increase in osmotic pressure produced by adding mannitol or sodium chloride in the medium surrounding trout fish induced an immediate but brief augmentation in cortisol release. the absence of Ca^{++} had no obvious effect while its addition induced an immediate peak of cortisol release. In addition, external Ca^{++} proved necessary for the action of ACTH to occur. These results establish that cortisol release in trout may be directly affected by changes in electrolyte concentration in the extracellular space.

In their studies, Gross, et.al., (1981) [illegible] sodium loading in both resulted in decrease in both [illegible] aldosterone and adrenal radiocholesterol uptake and that sodium depletion was associated with increases in both serum aldosterone and radiocholesterol uptake. these results were supported by Hamlet, et.al., (1987) who demonstrated that aldosterone cortisol ratio in normal subjects was unchanged or fell during saline infusion indicating an increase in cortisol level.

It is of a great value to mention that Junkergard and Augustinsson, (1990) showed a pronounced rise in plasma cortisol level elicited by i.v. infusion with 0.3M sodium chloride in man and by Angiotensin II in isotonic (0.15M) sodium chloride whereas Angiotensin II in glucose induces a smaller plasma cortisol rise.

AIM OF WORK

AIM OF THE WORK

Regarding the importance of isotonic saline in [illegible] research and clinical values.

This work aims to study the sodium chloride-induced metabolic changes and to investigate the possible relation of cortisol to these effects