# BIOCHEMICAL CHANGES AFTER VERAPAMIL ADMINISTRATION TO RATS TREATED WITH PROPRANOLOL

THESIS

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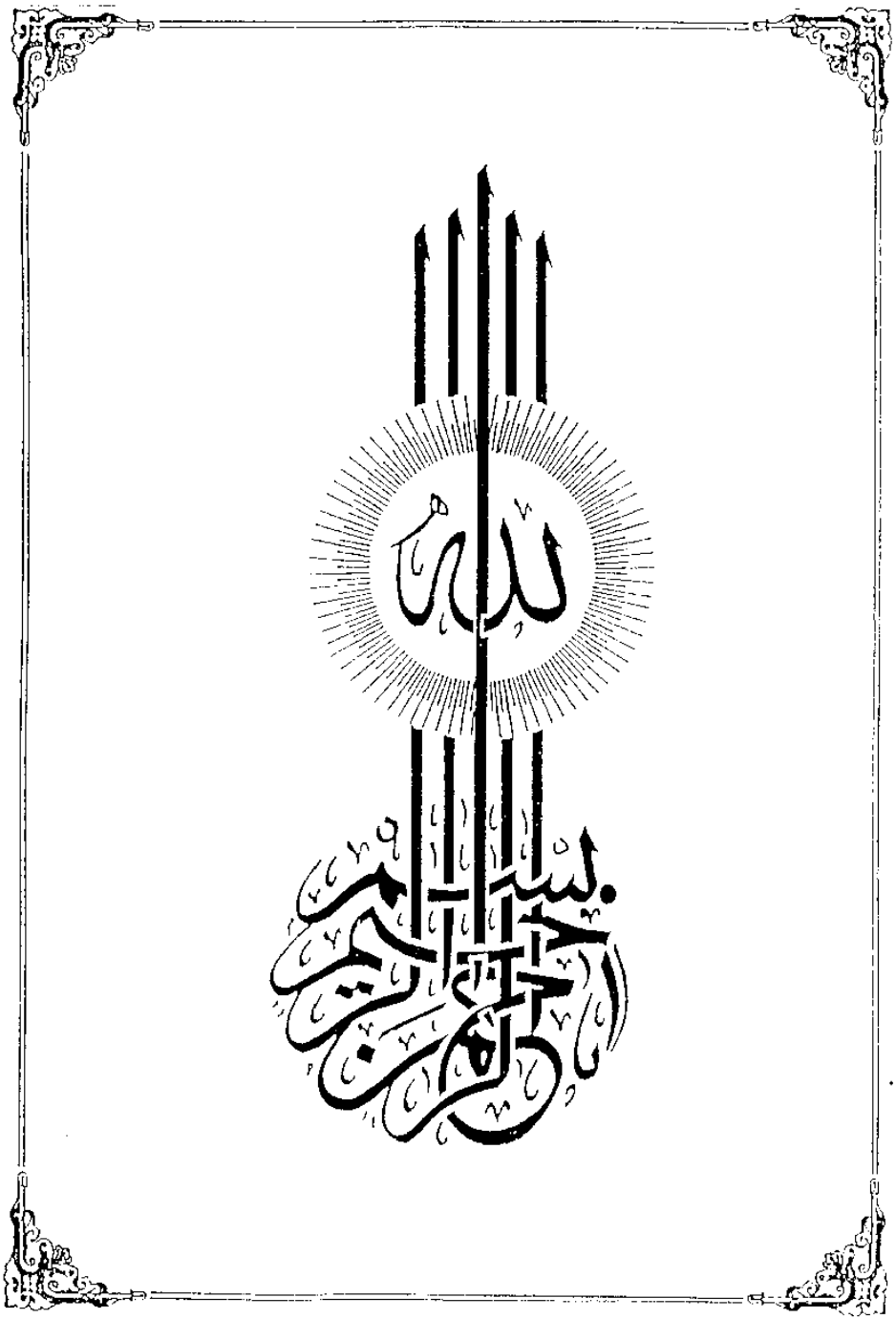
بسم الله الرحمن الرحيم

وقل رب زدني علما

صدق الله العظيم



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CONTENTS

# AIM OF THE WORK

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Verapamil is a famous drug widely used nowadays in clinical practice in a big group of cardiac patients.

On the other hand, B-blockers are a group of sympatholytic drugs which are also used in the same group of patients and both drugs may be given together.

This work aimed at studying the effect of verapamil administration to rats chronically treated with the B-blocker propranolol (inderal) on:

1- Blood glucose.

2- Serum alkaline phosphatase.

3- Serum transaminases.

4- Serum proteins.

# INTRODUCTION

## INTRODUCTION TO B-BLOCKADE

Alquist (1948) was able to classify sympathomimetic receptors into two groups, which he called alpha and beta; stimulation of which gives two distinct patterns of activity.

One pattern termed the alpha effects, includes contraction of smooth muscles such as vasoconstriction of blood vessels i.e. excitotory effects, with the exception of the $\alpha$-effect on the gut which is inhibitory.

The other pattern, which he named beta effects, includes inhibitory effects on smooth muscles, for example vasodilatation of skeletal and coronary blood vessels and excitatory effects on the heart.

The order of potency for stimulation of alpha-receptors was norepinephrine, epinephrine, methylnorepinephrine, methylepinephrine and isoprenaline; and for the beta-receptors was isoprenaline, epinephrine, methylepinephrine, methylnorepinephrine and norepinephrine.

The introduction of drugs with beta-blocking activity was started by Powell & Slater (1958) who described a compound, dichloroisoproterenol (DCI), which specifically blocked beta-adrenergic receptor sites.

Few years later propranolol was introduced into clinical practice by Black, et al. (1964) and it became widely used especially in anginose patients. Propranolol is a potent and specific B-adreno-receptor blocker, with no agonistic activity (no intrinsic sympathomimetic activity). It has a membrane stabilizing action (local anaesthetic action and quinidine-like action) (Welman et al, 1978).

It exerts a considerable antiarrhythmic effect on the heart which was thought to be partly due to its membrane stabilizing effect. However, Reimer et al (1976) demonstrated the inability of d-propranolol isomer to protect the myocardium although it possesses the same membrane stabilizing action on the myocardium as dl-propranolol (the racemic form commonly referred to as propranolol) but it lacks the B-blocking action. This suggests that the main effect is through B-blockade.

The serious side effect of propranolol on bronchi in the form of bronchospasm has stimulated an intensive research program aiming at the development of alternative B-blockers with cardioselectivity. This research lead to the discovery of many cardioselective beta-blockers which are now in clinical use e.g. metoprolol and atenolol.

However, this cardioselectivity proved only relative and dose-dependant, decreasing or disappearing altogether

by increasing the dose of the selective blocker (Louis et al, 1977; Imhof, 1974).

Even the concept that each tissue possesses a single receptor type ($B_1$-receptors in heart and $B_2$- receptors in bronchi and smooth muscles of blood vessels), as suggested by Land et al (1967) has been made false by Carlsson et al. (1977). He showed that most tissues examined possess both $B_1$ and $B_2$ receptors with relative proportions differing from tissue to tissue, from species to species and from individual to individual.

## STRUCTURE OF BETA-RECEPTORS

The possible structure of B-receptors has been the subject of much speculation. Suggestions have been made that beta-adrenergic receptors might actually be parts of adenylcyclase enzyme (Belleau, 1967).

Sutherland et al (1968) suggested that cyclic AMP might function as a "second mesenger", since its intracellular levels are influenced by a number of hormones. Lefkowitz and Levey (1972) proposed that the B-receptor might be a cleft in a protein attached to the external surface of the cell membrane and that adenyl cyclase is situated opposite it on the internal surface, and that a link between the two might be provided by a lipophilic briage or "coupling factor".

Recently Hirata & Axelrod (1980) showed that the binding of a catecholamine to the B-receptor, by a conformational change, would stimulate integral membrane enzymes; phospholipid methyltransferase I and phospholipid methyl transferase II which catalize the conversion of phosphatidyl-ethanolamine into phosphatidyl choline causing it to flip flop from inside toward the outside of the membrane.

The increased local concentration of phosphatidylcholine enhances local membrane fluidity to allow the occupied B-receptor to interact with the G.T.P.-dependant coupling factor and adenylate cyclase to activate the latter on the cytoplasmic aspect of the membrane.

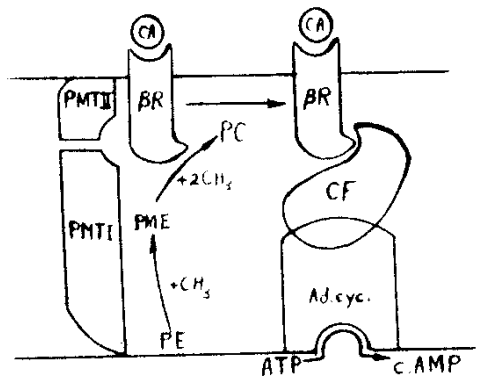
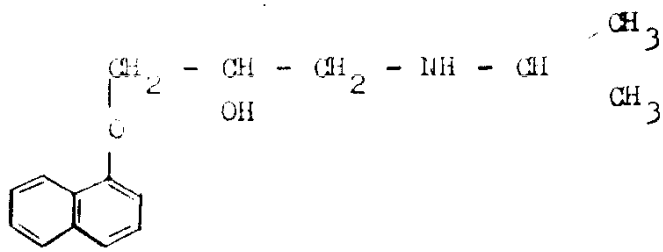



Fig. (1): Phospholipid methylation and B-adrenergic receptor coupling.

CA : catecholamine,
BR : B-adrenoceptor.
PMTI : Phospholipid methyltransferase I.
PMTII: Phospholipid methyltransferase II
PE : phosphatidylethanolamine
PME : phosphatidyl-N-monomethylethanolamine
PC : phosphatidylcholine
CF : coupling factor.
Ad.Cyc.: adenyl cyclase.

PROPRANOLOL



As all other B-blockers, propranolol is chemically related to and can be considered as a derivative of the B-receptor agonist, isoproterenol.

Pharmacological actions:

I- On the heart:

Nowadays, beta-adrenergic blockers are increasingly used in treatment of angina and they marked a significant step in the management of severe cases. (Hamer et al, 1964; Fitzgerald, 1969).

Black (1967) suggested, more than a decade ago, that the "anoxiating effects of adrenaline"during acute myocardial ischaemia could be opposed by B-adrenergic blockade.

Propranolol exerts a number of beneficial effects in acute myocardial infarction. It reduces oxygen requirements by decreasing heart rate and myocardial contractility and improves subendocardial perfusion in ischaemic myocardium (Vatner et al, 1977). It reduces catecholamine

induced lipolysis, thus favouring carbohydrate utilization (Opie, 1975). It shifts the oxyhaemoglobin dissociation curve to the right, promoting unloading of oxygen. (Lichtmant et al, 1974) and decreases the enhanced platelet aggregation characteristic of stress (Mehta et al, 1978 and Frishman et al, 1974).

II- On lipid metabolism:

Propranolol causes inhibition of catecholamine-induced lipolysis i.e reduces fat mobilization from adipose tissues and free fatty acids (F.F.A) release into the blood stream, particularly in everyday-stress situations. (Taggart et al, 1973).

This action is beneficial for various reasons:-

(1) The role of elevated plasma levels of F.F.A in the pathogenesis of atherosclerosis and coronary artery disease has been extensively documented particularly when associated with hypertension (Kannel, 1978).

(2) The increased F.F.A level in blood will increase F.F.A uptake and utilization by the myocardium and hence increases myocardial $O_2$ consumption (Lassers et al, 1971).