EXPERIMENTAL STUDIES OF SOME METABOLITES AFTER THE ADMINISTRATION OF VERAPAMIL AND DEXAMETHASONE INTO ALBINO RATS

THESIS

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M.Sc. Biochemistry

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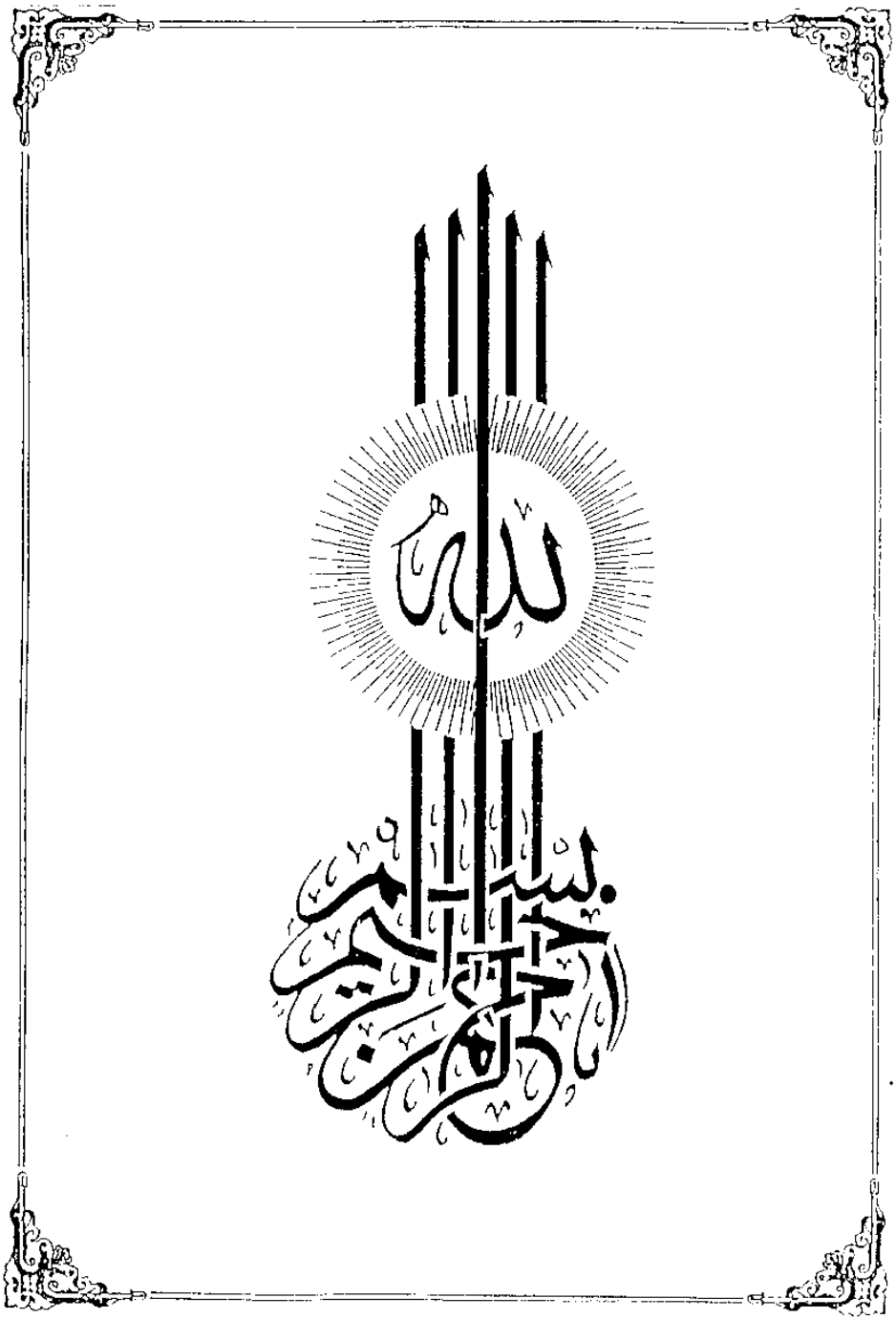
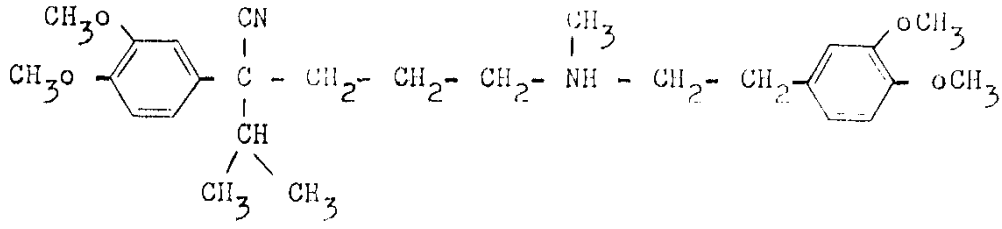


C O N T E N T S

INTRODUCTION

I N T R O D U C T I O N

Verapamil



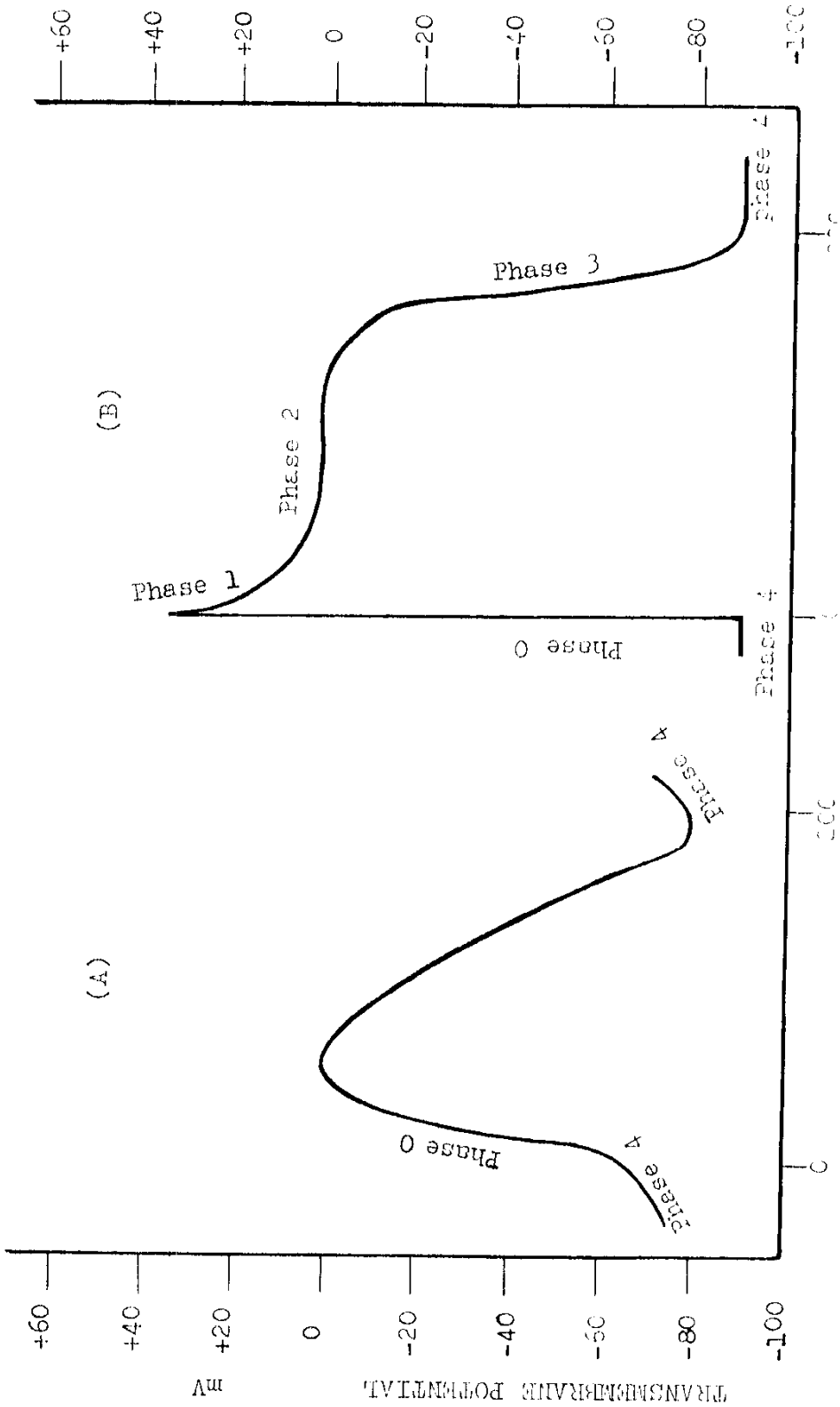
Verapamil was one of the two original compounds known as " calcium antagonists " . In fact, the group is more properly classified as calcium channel or slow channel inhibitors (Henry, 1980) .

This group of drugs was first discovered in 1963 and was considered to be vasodilator with no idea whatsoever about calcium channel or its blockade . Few years later, these drugs found their way to the treatment of several cardiovascular dysfuctions on the basis of calcium antagonism (Biekert, 1981) .

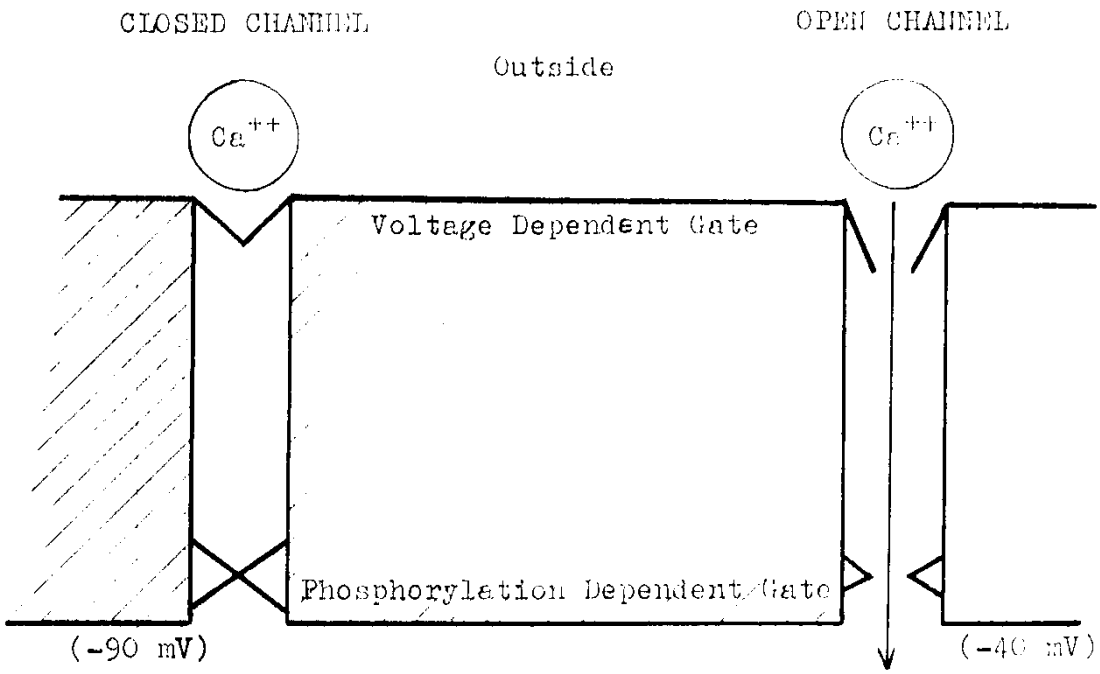
Mechanism of Action :

The mechanism of action of the slow channel inhibitors is generally considered to be interference with calcium ion flux across excitable membranes . This flux is responsible for the plateau phase (phase 2) of the action potential in excitable membranes and, indeed, almost the total depolarization action potential in sino atrial and atrioventricular nodal tissue (Antman et al., 1980) . This ion movement channel is referred to as " slow " in contrast to the " fast " sodium channel which is responsible for the rapid phase 0 and 1 depolarization in muscle and other excitable membranes (fig. 1)

For both channels, there appear to be at least two different loci of action . On the extracellular membrane surface is a voltage dependent gate which is either open or closed . Electrical depolarization of the membrane opens the gate and repolarization closes it . A second gate on the intracellular surface modulates ion flux . The major factor controlling the inner calcium ion gate is thought to be the cyclic nucleotides . Cyclic AMP facilitates widening of this gate and increases calcium ion flux, while cyclic GMP has the opposite effect (fig. 2). Verapamil appears to act via the inner locus (Coraboeuf, 1978) .

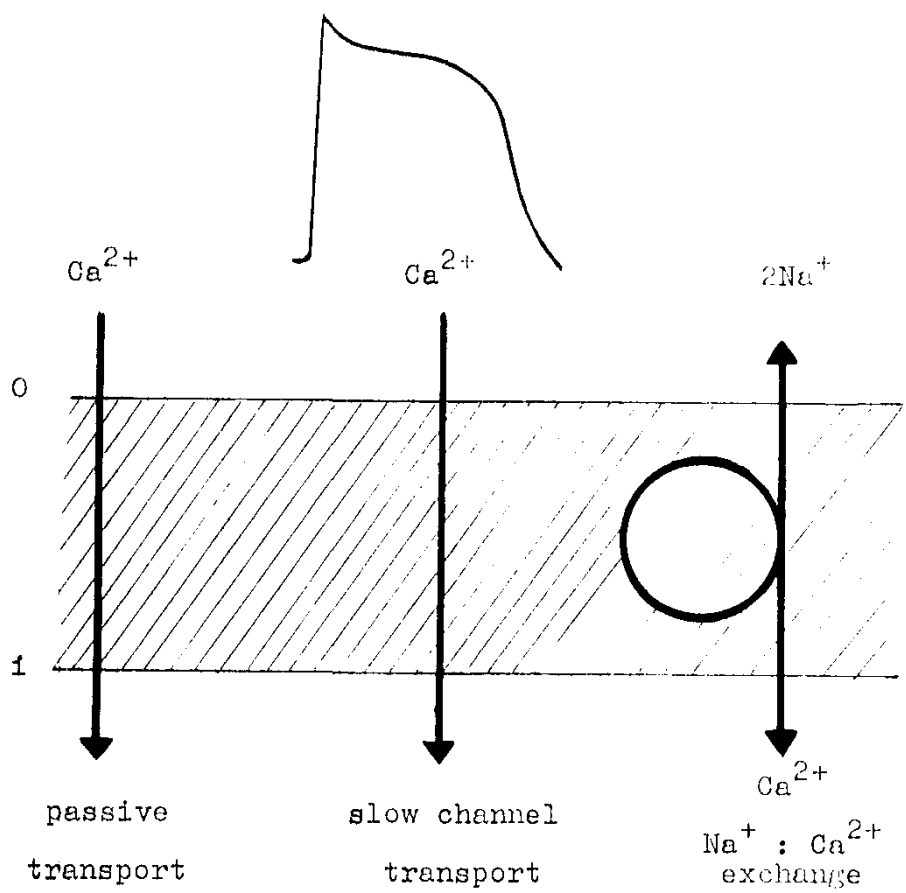


Figure(1): Typical Action Potentials of:
(A) SA Nodal Cells, and
(B) Ventricular Myocardium.
(Antman et al.,1980)



Figure(2): Schematic Model of a Slow Calcium Channel.

(Coraboeuf,1978)



Figure(3): Schematic Representation of the Three Ways in Which Ca^{2+} Can Penetrate the Cell Membrane. (Nayler,1981)

If the inward displacement of calcium during the plateau phase of the action potential was the only mechanism whereby calcium ions penetrate cardiac muscle and other excitable cells, the continued use of the term " calcium antagonists " to describe the action of drugs of the Verapamil type might be justified . There are however, at least two other ways in which calcium ions can cross cell membranes; by passive exchange and via a calcium-sodium exchange mechanism which involves the exchange of one calcium ion for two sodium ions . It is because the effect of the verapamil type of drugs on calcium transport is restricted to that component of calcium transported inward during the plateau phase of the action potential that the term " inhibitors of the slow calcium channel " may more accurately describe the mode of action of these drugs (Nayler, 1981)

Precisely how calcium antagonists exert their effects is still not known . Many, including verapamil, are lipophylic . It is possible, therefore, that they react with hydrophobic residues in the cell membranes, thereby producing a conformational change which in turn alters either the calcium transporting or calcium storing capacity of these membranes (Nayler, 1981) . In

heart muscle an action of these drugs on the calcium storing capacity of the cell membrane might also be of importance because there is some evidence that the calcium ions which enter the cell during the plateau phase of the action potential do not originate directly from the extracellular phase but rather from superficially located depots, located close to or on the outer surface of the cell membrane. Recent experiments on isolated cell membranes of heart muscle have shown that their ability to bind Ca^{+2} is significantly reduced even after only relatively short periods of incubation in the presence of micromolar concentrations of verapamil (Nayler, 1981) .

In a study on model membranes (Neyroz et al., 1980) data were obtained suggestive of partition equilibrium of verapamil between the membrane and the aqueous medium. Whether verapamil pharmacological activity is due to its interaction with membrane components or with calcium still needs to be elucidated .

The effect of verapamil was studied on isolated cardiac sarcolemmal preparations . Verapamil inhibited the passive binding of calcium ions to the membrane . It also inhibited the ATP-dependent transport of Ca^{+2}

and the associated activation of the Ca^{+2}-sensitive ATPase . Enzymatic removal of N-acetyl neuraminic acid and galactose residues increased verapamil binding to the memorane, while removal of N-acetyl glucosamine and treatment with phospholipase C and trypsin decreased the binding . (Mas-Oliva & Nayler, 1980) .

Pharmacokinetics :

Orally administered verapamil is rapidly absorbed. Unfortunately, there is extensive evidence of first pass metabolism in the liver, resulting in the formation of two inactive and one relatively active metabolites (Nayler, 1981) . This first pass metabolism reduces the bioavailability of verapamil by about 80 or 90% and could easily account for the well documented discrepancy between the effectiveness of the oral and intravenous routes of administration . In addition to its rapid first pass metabolism, verapamil undergoes extensive binding to plasma proteins . In the plasma the drug appears to be distributed between two compartments, one with a half decay time of about 20 minutes and the other with a half decay time of 200 - 400 minutes (Nayler, 1981) .

Pharmacological actions :

Calcium ions are necessary for several biological functions performed by living cells . Muscular contraction,

ple, is totally dependent on calcium . It is
that calcium channels are located in the T-tubules
arcolemma, and the influx of calcium triggers the
of stored calcium from the terminal cisterns of
smic reticulum . Calcium then binds to troponin C
rates myosin-ATPase causing sliding of actin
over myosin with shortening of the sarcomere .
, inhibiting the calcium influx, will lessen
calcium ions activating the contractile system
ease in the force of contraction (Nayler & Krikler,
This will be accompanied by a decrease of
mand of the myocardium . There will be also
ion of the coronaries, increasing the blood supply
ocardium . At the same time, decrease of peri-
scular tone will decrease the after load and
done by the heart . Thus, verapamil is of highest
l value in cases of coronary insufficiency
y the spastic type (Check, 1981) .

place of calcium antagonists among commonly
ypertensive medications has not been fully
With their known pharmacologic effects, both
yocardium and vascular smooth muscle cells,
to be given a fair chance of several clinical
ore we can judge whether they will or will not

have such a place in the field of hypertension drugs (Saad, 1981) .

As calcium ion influx is responsible for the slow diastolic depolarization in nodal cells, verapamil as would be expected can slow the rate of this depolarization, thus normalizing a rapid rate heart . In fact, it has been successfully used in the treatment of paroxysmal supraventricular tachycardia and some other arrhythmias (Check, 1981) .

Since the presence of an inward calcium current is not peculiar to cardiac muscle cells, one can expect that drugs of the verapamil type should affect the functioning of many different cell types (Nayler, 1981) . In fact, the role of calcium in stimulus-secretion coupling has been established in a variety of tissues (Rasmussen & Goodman, 1977) . It has been proved that stimulation of Ca^{+2} uptake is associated with the stimulation of catecholamine release by acetylcholine in the adrenal medulla (Serck-Hanssen & Christiansen, 1973) . Also, stimulation of Ca^{+2} uptake is associated with the stimulation of carbamyl-choline-induced enzyme release in the parotid gland (Kanagasuntheram & Randle, 1976). It is now well known that verapamil inhibits calcium