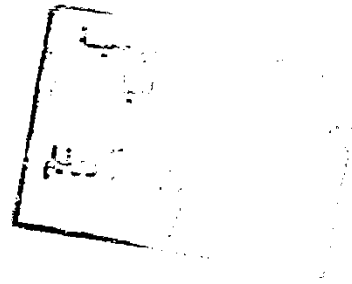
CALCIUM CHANNEL BLOCKERS IN NEUROLOGY AND PSYCHIATRY

Master degree thesis submitted for partial fulfilment of the master degree in neuropsychiatry

By

Magued Ernest Riad

M.B. B. Ch.



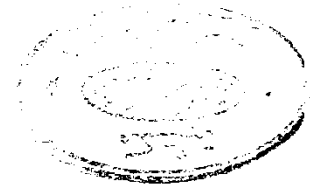
Supervised by

Prof. Dr. Youssef Ali Abu Zeid

Professor of Neurology

Faculty of Medicine

Ain Shams University



Ass. Prof. Mohamed Hamed Mohamed Ghanem

Ass. Prof. of Psychiatry

Faculty of Medicine

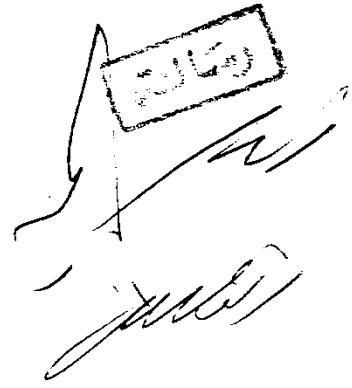
Ain Shams University

Dr. Samia Ashour Mohamed

Lecturer of Neurology

Faculty of Medicine

Ain Shams University



Faculty of Medicine

Ain Shams University

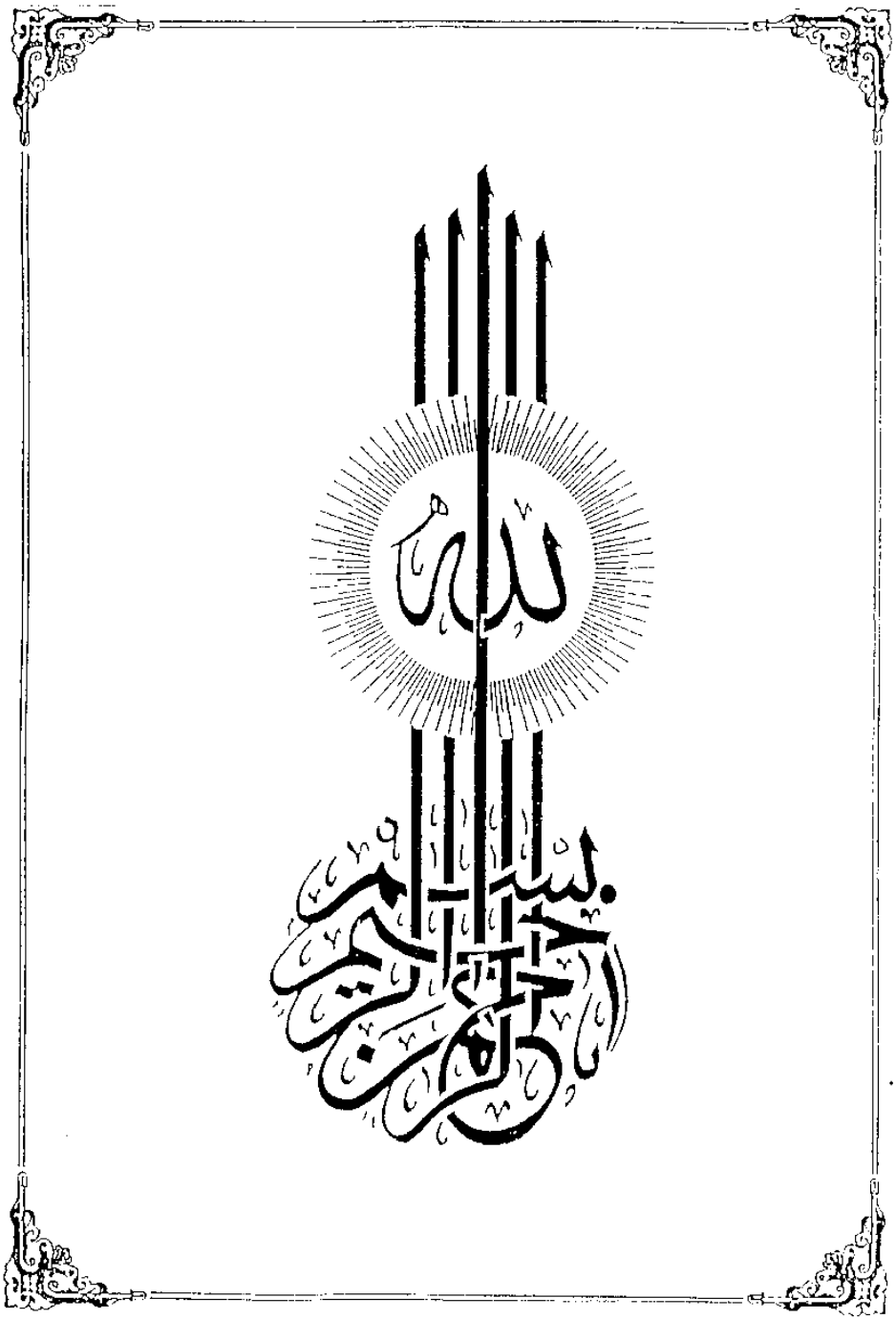
1993

ACKNOWLEDGEMENT

Firstly, I would like to thank **Prof. Dr. YOUSSEF ALI ABU ZEID** for his valuable help and continuous guidance.

I would like to express my most sincere thanks and deepest appreciation to **Ass. Prof. Dr. MOHAMED GHANEM** and to **Dr. SAMIA ASHOUR** lecturer of neurology for their support and guidance of every stage of this work.

MAGUED ERNEST



CONTENTS

INTRODUCTION

CHAPTER 1

Pharmacology and Mechanism of Action of Calcium Channel Blockers

INTRODUCTION

1. Calcium channel blockers have recently been found to have a possible useful role in Neurology and Psychiarty.
2. Calcium chnnel blockers have been used as prophylactic therapy in migraine and 80% of patients got benefit from them **(Solomon et al 1983).**
3. Calcium channel blockers have been used in prevention of cerebral vasospasm after subarachnoid haemorrhage **(Allen et al 1983).**
4. Flunarizine stabilises the cell membrane for Ca++ flux and blocks the spread of seizure activity **(Overweg et al 1984).**
5. Verapamil was proved to be effective as antimanic drug in the treatment of a manic patient. **(Dubovsky et al 1982).**

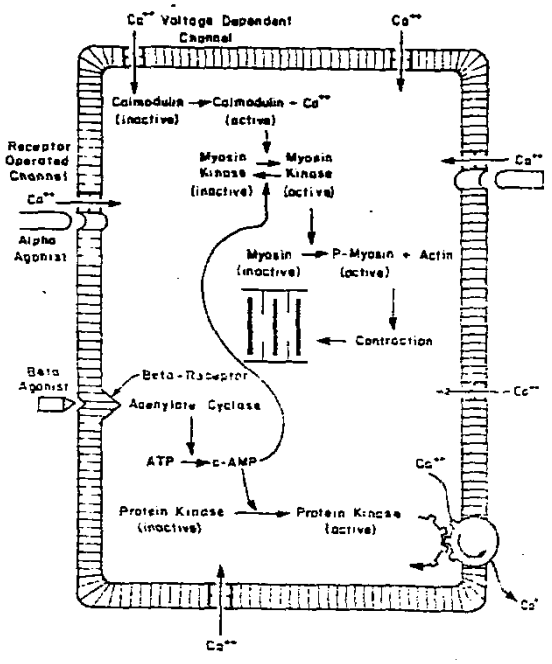
AIM OF WORK

The work aims to review the literature of action of calcium channel blockers in neuropsychiatric disorders inorder to clarify the machanism of action and role of it in prevention of cell damange, vascular system, psychiatric disorder to assess specific effects of each of them in migraine, epilepsy, ischemia, psychiatry and to evaluate the prognosis.

ROLE OF CALCIUM IN THE BRAIN

AND IN VASCULAR SMOOTH MUSCLE CONTRACTION

A) Calcium ions are vital in many biologic processes, including a variety of enzymatic reactions, activation of excitable cells, coupling of electrical activation to cellular secretion, hemostaasis, and the metabolism of bone. Actin is a globular protein that polymerizes to form a double helical filament - the thin filament. Myosin is a hexamer with one pair of heavy chains and two pairs of light chains arranged in parallel to form a thick filament. Projections of a portion of the myosin molecule arise from the thick filaments at regular intervals. Contraction of all forms of muscle is an energy - requiring cyclic process in which this globular portion of the myosin molecule attaches to and detaches from the actin filament. Muscular relaxation results from cessation of the influx of Ca++ into the cell, coupled with the reuptake of Ca++ by the secrocplasmic reticulum. (Braunwald 1982). The process that regulates contraction in vascular smooth muscle results from a cascade of reactions, the first of which involves a small Ca++ binding protein called Calmodulin. When Ca++ in the vascular smooth muscle rises to approximately 10^{-6} M, Ca++ binds, to calmodulin, and the Ca++ - calmodulin complex activates the enzyme myosin kinase; this in turn phosphorylates a light chain of myosin, which permits myosin to interact with actin, thereby leading to contraction of the muscle cell and arteriolar constriction. **(Braunwald 1982).**



The Role of Calcium (Ca^{++}) in Vascular Smooth Muscle. Ca^{++} can enter the cell through voltage-dependent channels; additional receptor-operated Ca^{++} channels can be recruited as a consequence of activation of alpha-adrenergic receptors in the sarcolemma. Activation of beta receptors results in a reduction of intracellular [Ca^{++}] through two possible mechanisms, both dependent on cyclic AMP. P denotes phosphorylated.

Ca++ CAN CROSS THE SARCOLEMMA:

1) The first is the inward movement of Ca++ along its concentration gradient.
2) Evidence for a bidirectional Na+ - Ca++ exchange system.
3) When a propagated wave of depolarization approaches the membrane region containing the Ca++ channel, reduction of membrane potential (a decrease in the electronegativity in the cell interior) causes the activation gate to open, permitting Ca++ to cross the membrane and pass into the cells.

   The movement of Ca++ through these channels is controlled by electrical potentials, they have been termed "Voltage-dependent" channels.
4) Adrenergic influences increase Ca++ influx ; the channels acted upon by receptor-mediated events are termed "receptor-

operated" channels. (Braunwald. 1982)

B) In exitable tissues, calcium is a first and second messenger and a regulator of metabolic pathways, serving to transform external messages into the appropriate cellular metabloic responses. Synaptic activation in the brain involves the release of an excitatory transmitter, usually glutamate, which triggers "fast" excitation by activating a postsynaptic Na+ conductance resulting in depolarization. While the depolarization may be sufficient to carry the message of excitation from pre to postsynaptic sites, Calcium is required to elicit metabolic reactions, which among other things form the basis of memory formation.

Voltage sensitive calcium, channels, were considered to constitute the major entry route for calcium, the channels being opened in response to depolarization of pre and postsynaptic membranes and blocked by calcium antagonists of dihydropyridine (DHP).

It was reported that peripheral neurons contain 3 different voltage- sensitive calcium channels, L (long-lasting), T (Transient) and N (Neither L nor T) of which only one (The L type) is considered sensitive to calcium antagonists of DHP type, (N) type of channels may be one mediating presynatpic calcium influx, causing transmitter release, (L) type of channel has been found localized to , among other structures, postsynaptic membranes (central dendrites and some membranes), it may be involved in relaying postsynaptic calcium currents. (Siesjo, 1990).

There is no doubt that voltage sensitive calcium channels

exist in brain neurons and that they mediate fluxes of calcium from extracellular fluid to intracellular fluid, however, the major postsynaptic calcium channel., probably localized to dendritic spines and apical dendrites is an agonist operated calcium channel which is activated by glutamate and related excitatory amino acids.

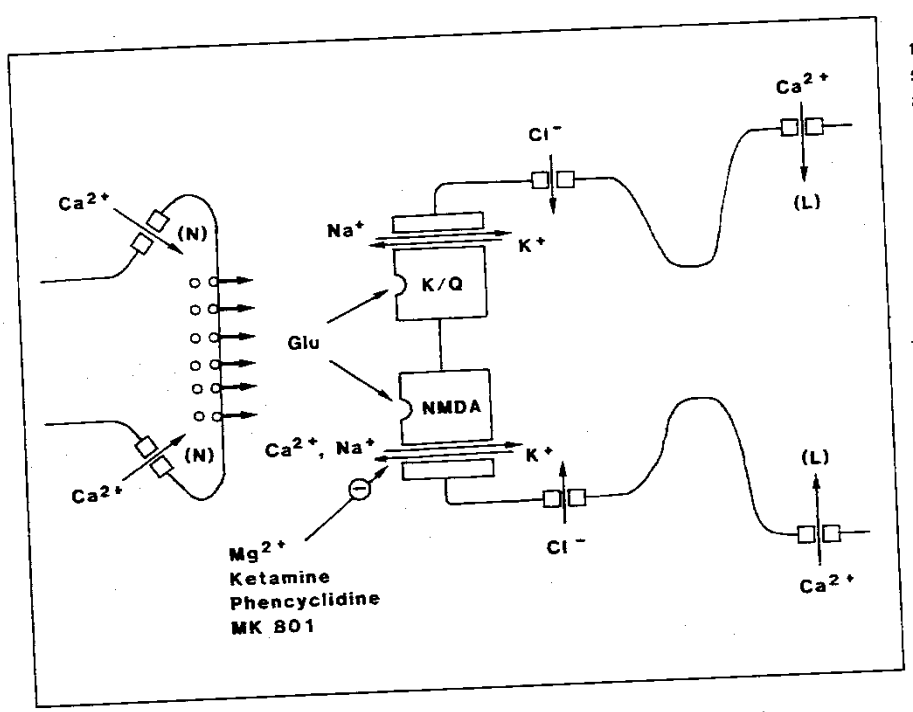
Glutamate activates 2 major types of ionotropic receptors, one of them which is selectively acitvated by the glutamate analogues kainate (K) & quisqualate (Q) , is linked to a channel which is permeable to monovalent cations (Na+, K+, H+) the other receptor, selectively activated by N-methyl D-aspartate (NMDA) is linked to a channel which is permeable, not only to monovalent cations, but also to calcium. This is a high conductance channel responsible for the influx of calcium, glutamate activation of the receptor & influx of calcium are strongly potentiated by low concentration of glycine and inhibited by Zn^{2+}, furthermore, the channel is blocked by Mg^{2+} in physiological concentrations. This block is relieved when the membrane depolarizes, meaning that 2 things are required for calcium entry : glutamate activation of the receptor and depolarization. **(Siesjo, 1990).**

Blockers of agonist operated Calcium channels (AOCCs) are generally more efficacious in ameliorating ischemic brain damage, probably because they impede calcium influx into dendritic domains.

Intracellular calcium release occurs from endoplasmic reticulum (ER) and other sites (Calciosomes) in response to release of inositol triphosphate (IP_3) and to administration

of Caffeine.

At least some neurons show <u>Calcium-dependent calcium release</u> i.e. influx of calcium can cause intracellular calcium release, contributing to the rise in Ca++, such reactions may be part of a positive feed back loop, which amplifies the initial response, however the rise in Ca^{2+} also triggers the extrusion of calcium from the cell, or its sequestration within the cell. Calcium is extruded by a low-capacity - high affinity ATPase which is calmodulin dependent and by high capacity - low affinity 3 Na^{+} / Ca^{2+} exchanges which utilizes the energy stored in the Na+ gradient to expel calcium. (SIESJO 1990)



Ionic fluxes in presynaptic and postsynaptic structures. Presynaptically, transmitter release is assumed to be triggered by calcium, entering by an N type of VSCC. Postsynaptically, an L type of VSCC, perhaps localized to central dendrites and soma, may mediate calcium influx. However, AOCCs are the major contributors to postsynaptic calcium entry, the majority being gated by glutamate receptors. These are of two main types: K/Q-preferring, and NMDA-preferring. The former is linked to a channel which allows monovalent cations to pass, while the latter is permeable to calcium as well. Inhibition occurs by activation of Cl^{-} and K^{+} conductances which are, at least in part, calcium-activated. The NMDA-linked channel is blocked by Mg^{2-} in physiological concentrations, by ketamine, by phencyclidine and by related compounds.

CALCIUM CHANNEL BLOCKERS

CLASSIFICATION ACCORDING TO

MECHANISM OF ACTION

There are different terminology such as calcium inhibitors, calcium blockers, calcium entry blockers and calcium channel blockers, calcium antagonists. (Albrecht 1987).

The term Calcium antagonists is maintained for historical reasons, although calcium entry blockers, calcium channel blockers or other comparable terms are more correctly because they block the entry of calcium into the cell instead of antagonizing the action of the Ca++ ion (Agnoli 1988).

CLASSIFICATION:

A - Selective for slow Ca^{++} channels:

Class I Verapamil like (Phenylalkylamines e.g. Verapamil, gallopamil).

Class II Nifedipine like (Dihydropyridines e.g. Nifedipine, nicardipine, nimodipine).

Class III Diltiazem like (Benzothiazepines, Diltiazem).

B - Non Selective for slow Ca^{++} channels:

Class IV Flunarizine like (Diphenylpiperazines e.g. Flunarizine)

Class V Prenylamine like (e.g. Prenylamine , Fendilline).

Class VI Others (e.g. Bepridil, Caroverine, Perhexilline).

IT SHOULD BE NOTED THAT :

ONLY CLASS I TO IV AGENTS were presumed to act primarily by inhibiting the entry of calcium into the cells. Substances of calss V , VI interact at similar concentrations with fast sodium channels.

ALL CALCIUM ANTAGoNISTS are able to inhibit vasospasms induced by vasocontricitve agents such as noradrenaline, serotonin, thromboxane, etc., or induced by high potassium concentrations through inhibition of potential and receptor operated Ca++ channels of vascular smooth muscle cells.

THE MYOGENIC ACTIVITY OF VASCULAR smooth muscle cells maintain the normal peripheral resistance tonus of blood vessels, only flunarizine like substances spare the myogenic activity of vascular smooth muscle cells. Class IV substances therefore do not induce vasodilation, so class IV agents affect blood pressure only to a minimal extent. A drop in blood pressure may be contraindicated in the acute treatment of cerebrovascular accidents (Agnoli 1988).

Ca CAHNNEL BLOCKERS ARE USED IN NEUROPSYCHIATRIC DISORDERS OF THE FOLLOWING CONDITIONS:

1. As prophylaxis of migraine, vertigo.
2. Against cerebral vasospasm in subarachnoid haemorrhage.
3. Antiepileptogenesis.
4. Ischemia and infarction.
5. Vertebrobasilar transient ischemic attacks.

6. Familial periodic ataxia
7. Psychiatry especially mania and tardive dyskinesia.
8. Hypertensive encephalopathy.