BETA-ADRENOCEPTOR BLOCKING DRUGS IN SURGICAL PRACTICE

THESIS

Submitted For The Partial Fulfillment
Of Master Degree In
GENERAL SURGERY

BY

WAGIH LAMIE BASTA

M.B., B. Ch.
Ain Shams University

SUPERVISED BY

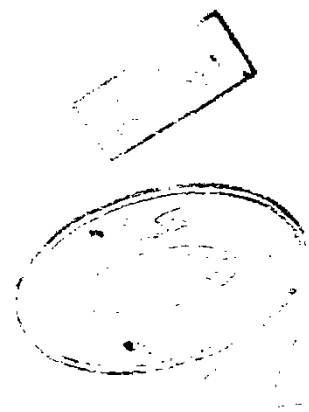
Prof. Dr. REFAAT KAMEL
Professor of General Surgery

Dr. ALAA ELDIN ISMAIL
Lecturer of General Surgery

Faculty of Medicine
Ain Shams University

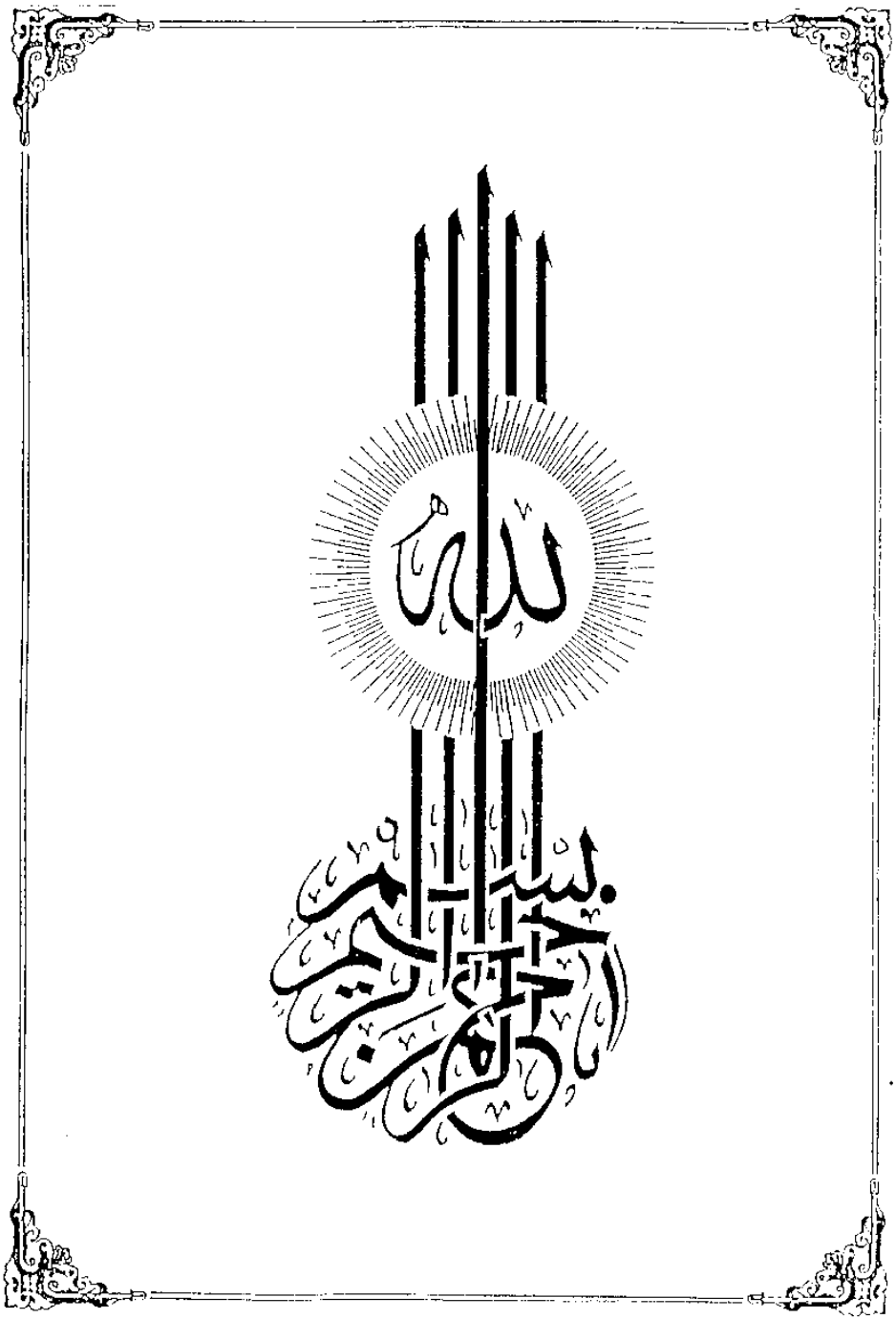
1985

Maktab El-Shark, Zagazig



TO

MY PARENTS



ACKNOWLEDGEMENT

I wish to express my deep, sincere gratitude to Prof. Dr. REFAAT KAMEL *Professor of General Surgery, Ain Shams University, for his enthusiastic teaching and constant encouragement, supervision and revision of this work. He is a great example to be proudly followed.*

I also want to express my deepest thankfulness to Dr. ALAA EL DIN ISMAIL *Lecturer of General Surgery, Ain Shams University for his unique Co-operation, and his continuous guidance, suggestion and assistance, without which this work would not have come to light.*

I am thankfull to my wife for her help and many sacrifices.

W. L. BASTA

CONTENTS

INTRODUCTION

The development of the beta-adrenoceptor blocking drugs can be considered one of the landmarks in the history of the pharmacologic research.

The introduction of beta-adrenoceptor blocking drugs to the field of clinical medicine has provided one of the major triumphs of this century. The pioneers of this field hypothesized that beta-adrenoceptor blockers would be beneficial in the treatment of angina pectoris, but they could not foresee the large spectrum of their therapeutic indications that are now being discovered. Beta-adrenoceptor blockers are used now with success in the management of a wide variety of disorders as thyrotoxicosis, portal hypertension and myocardial infarction. Beta-blockers were not discovered by chance, they were synthesized by Black and his colleagues working at Imperial Chemical Industries (ICI) in England (1). Dichloro-isoprenaline (DCI) was the first synthesized beta-adrenoceptor blocking drug and it had potent intrinsic sympathomimetic activity and increase the resting heart rate. (2) D C I was not clinically useful because of its toxicity by virtue of its adrenaline like action (3). The first derivative that I.C I developed was pronetholol. Although a more potent beta-adrenoceptor blocking drug than D C I , pronetholol has intrinsic sympathomimetic

activity. The undoubted clinical potential of pronetholol was not achieved because the new drug was found to produce tumours in mice that had received high dose for a long period of time. ICI were able to replace pronetholol with propranolol, that was definitely not carcinogenic and did not have any intrinsic sympathomimetic activity. (3) Within the last two decades, a long list of new members of beta-adrenoceptor blockers is provided. This contain acebutolol (Sectral), atenolol (tenormin), metoprolol(lopresor), oxprenolol (trasicor), pindolol (Visken), practolol (Eraldin), propranolol (inderal), sotalol (Sotacor), timolol (Blocarden), nadolol (Corgard), and labetalol (trindate). (4)

The aim which stimulated the synthesis of these agents was the search of members which are specific to the organ wanted, with heigher efficacy and least side effects. Most of these drugs are available now to the clinicians in many counteries. In the United States, until 1983 only atenolol, metoprolol, nadolol, pindolol, propranolol and timolol are approved by Food and Drug Administration for use in hyper-tension. Several others are presently undergoing active clinical investigations in U.S.A. (5) The members of beta-adrenoceptor blockers appear to have the same useful and adverse effects. However differences in pharmacologic

properties as intrinsic sympathomimetic activity, membrane stabilizing, potency, metabolism and passage through blood brain barrier may prove clinically of importance. With introduction of beta-blockers into clinical practice problems arose as in patients with peripheral vascular disease leading to stimulation of trials in cardioselective members. Similarly propranolol with high doses and frequency of administration in case of hypertension stimulated the trials in members with prolonged action which can be given once or twice daily. Combination of beta-adrenoceptor blocking drugs with diuretics and a beta-blocker with a weak alpha blocking effect (labetalol) are now also available. (4).

CHAPTER I

RECEPTORS

The concept of pharmacologic receptors is approximately 75 years old. Although it was not until 1948 that Ahlquist classified adrenoceptors as alpha or beta.

However Dale was the first to make significant use of the receptor concept in connection with the sympathetic nervous system. From the work of Dale it was known that ergot alkaloids prevented only the motor (excitatory) action of epinephrine (6). Evidence favoring the existance of receptors is overwhelming and the cholinergic receptors have been successfully isolated.

Receptors are defined as the specific cellular structures with which drugs and hormones first interact. They may be located intracellularly or at the cell surface. Only molecules that can bind to the receptors by virtue of some complementarity in structure between receptors and drug will be active. Once such binding has occured, a biologic process may or may not be stimulated depending on whether an agonist (receptor stimulating drug) or an antagonist (receptor blocking drug) has occupied the receptors.(7)

The groups in the drug combining to the binding site of the receptor are called (Ligands).

The receptor along with the molecules involved in the multistep sequential reaction comprise the "pharmacologic receptor system".

The adrenergic receptor system has been the subject of a plethora of publication. Binding to adrenergic receptor by agoinst is usually followed by activation of the enzyme adenylate cyclase, located on the inner surface of the cell membrane. This enzyme catalyses the conversion of A T P to cyclic A M P which called "Second messenger". On the other hand alpha receptor stimulation decreases cyclic A M P. (8) Sutherland and his colleagues developed the now widely accepted theory that the link between receptor binding and biologic response often was to be found in the form of so called "Second messengers" such as cyclic 3' 5'- adenosine monophosphate and other cyclic nucleotides. Cyclic A M P appears to activate a class of enzymes known as protein kinases, which phosphorylate a wide variety of important substrates, which in turn appear to mediate the characteristic responses attributed to many drugs and hormones (9). Although the receptor hypothesis had its roots in the early work of Langely (1905) and Clark (1937), yet, it was not significantly

appreciated by pharmacologists, until 1948, when Ahlquist published his classic paper on adrenergic receptors. He introduced the concept of α and β-adrenergic receptor to explain the action of a series of sympathetic amines on various smooth and cardiac muscle. (6)

It was appreciated very early that various subclasses of receptor existed. Now it is generally accepted that beta-adrenergic receptors fall into distinct subclasses. The existence of distinct B-adrenergic receptor subtypes termed B_1 and B_2 was first postulated by Lands and co-workers. (10) This classification was based on the rank order of potency of a series of drugs in eliciting biological responses. (11) This differentiation into B_1 and B_2-adrenergic receptors has resulted in a classification of tissues into B_1-adrenergic tissues, such as the adipose tissue (Lipolysis) the jejunum (relaxation) and the heart (force and rate), these tissues are particularly sensitive to norepinephrine, and tissues predominantly B_2-adrenergic in nature, which are particularly sensitive to epinephrine, such as striated muscle (lactic acid production), the uterus (relaxation) and the bronchial tree (relaxation). (12)

The concept now is that B_1-adrenoceptors are located primarily on the myocardial cell membrane, although some

investigators suggest that there are B_1-adrenoceptors in the kidney that mediate, at least in part, neurally generated release of renin. the B_2-adrenoceptors are located on the cellular membranes of other organs including the bronchi, G I T, uterus and skeletal muscle. (5)

Moreover, B_1 and B_2-adrenoceptors may occur side by side and in varying proportions in various tissues (12).

The distribution of adrenergic receptors and the responses that occur when they are activated are shown in table (1), and figure (1). In general the effect of activation of α-adrenoceptors in smooth muscle is excitatory, while that of B_2-adrenoceptors at such sites is inhibitory, although this is not an absolute rule. In other tissues, B-adrenoceptors can mediate stimulatory effects.

More recently a third type of adrenergic response termed dopaminergic has been defined. These responses are most potently stimulated by the norepinephrine precursor dopamine. Dopaminergic receptors are found in certain brain regions and also in the renal vasculature, where they apparently cause vasodilatation. (7)

Most recently investigators have directly probed these receptors by using radioactively labeled hormone and drug

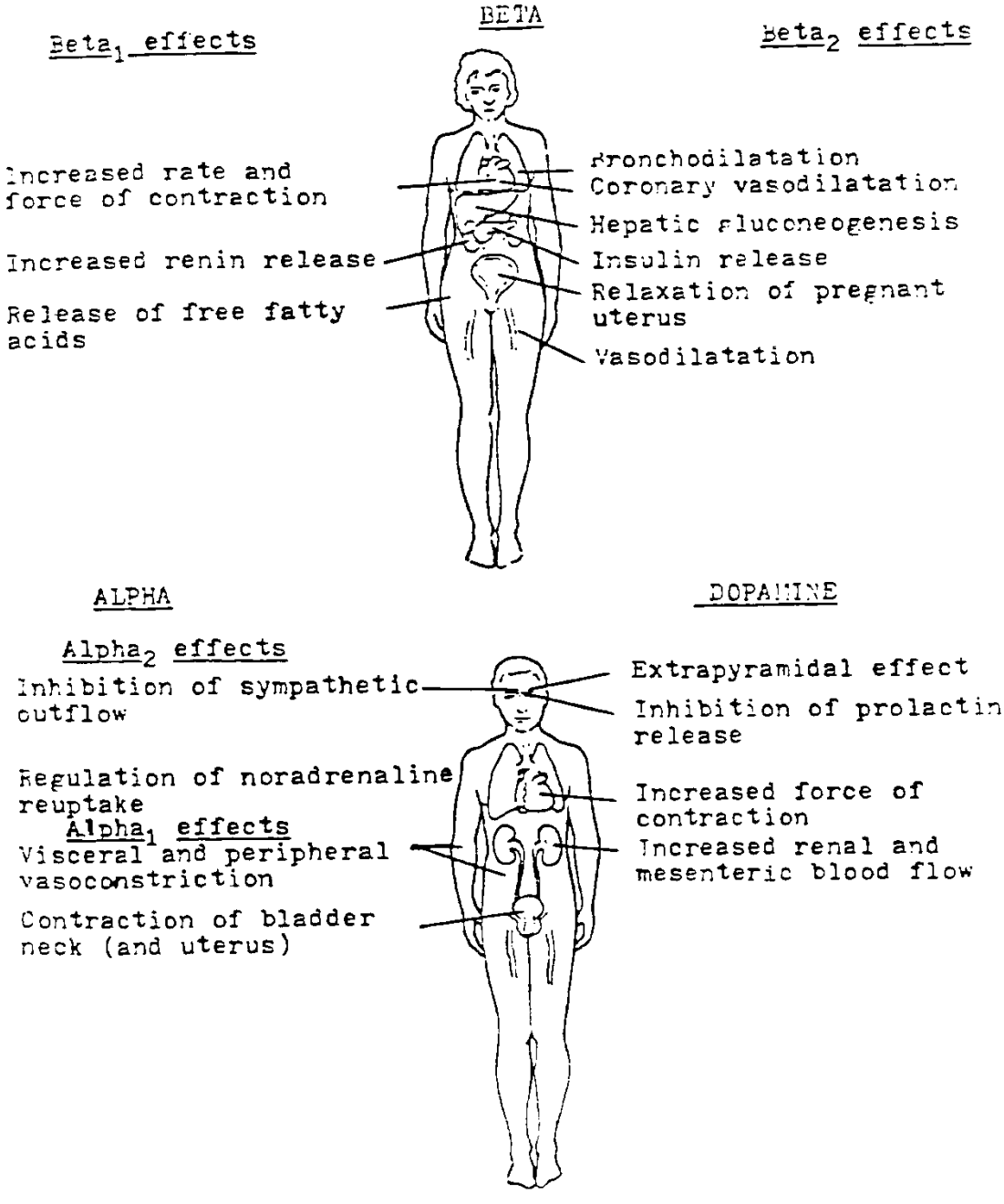
derivatives, termed radioligands, which have greatly aided the investigation of adrenoceptors, their physiologic regulation and their molecular properties. (13).

According to Lefkowitz (7) continuous exposure of tissue to catecholamines leads to refractoriness or desensitization. This is accompanied by marked alteration in B-adrenoceptors with comparable reduction in their numbers. An up-regulation (elevation in the number of receptors) of Cardiac B-adrenoceptors was observed by Glaubiger and Lefkowitz after chronic treatment of rats with propranolol (15). This may be associated with hypersensitivity of the beta-adrenergic receptors to agonist and may explain the "withdrawal effects" which occur in patients with ischaemic heart disease upon sudden cessation of therapy with beta-adrenoceptor blockers. (2).

Receptor density is decreased with ageing, so that an initial small dose of beta-blockers in the elderly should be cautiously increased, especially in view of the possibility of impaired cardiovascular function (1).

The number of Cardiac B-adrenoceptors have been shown to increase in hyperthyroid animals and decrease in hypothyroid animals, (16) and this may explain the beneficial effects of B-adrenoceptor blockers in these diseases.

Figure (1): Effects of stimulation of the sympathetic system:



From Feely et al., 1983 (4).

Table 1 – *Responses mediated by adrenoceptors*

Cell, organ, or system affected	Adrenoceptor type	Response
Heart	$\beta_1 > \beta_2$	Increased automaticity
	β_1	Increased conduction velocity
	β_1	Increased excitability
	β_1 (?also α)	Increased force of contraction
Blood vessels	α	Constriction of arteries and veins
	β_1	Dilatation of coronary arteries
	β_2	Dilatation of most arteries
Lung	α	Bronchoconstriction
	$\beta_2 > \beta_1$	Bronchodilatation
Skeletal muscle	β_2	Increased force and duration of contraction of fast contracting muscle, decreased force and duration of contraction of slow-contracting muscle (hence tremor)
Smooth muscles:		
Uterine muscle	β_2	Relaxation
Eye	α	Mydriasis
Intestinal muscle	β_1	Relaxation
Mast cells	α	Augmentation of release of mediators of anaphylaxis
	β	Inhibition of release of mediators of anaphylaxis
Platelets	α_2, β	Aggregation promoted
Metabolism:		
Gluconeogenesis	α	Promoted
Glycogenolysis	α (liver)	Promoted
	β_1 (heart)	Promoted
	β_2 (skeletal muscle)	Promoted
Lipolysis (white adipocytes)	Beta$_3$	Promoted
Calorigenesis (brown adipocytes)	β_1	Promoted
Hormone secretion:		
Glucagon	β_2	Promoted
	α	Inhibited
Insulin	β_2	Promoted
Parathyroid hormone	β	Promoted
Renin	β_1	Promoted
Neurotransmitter release:		
Acetylcholine	α	Facilitated (skeletal neuromuscular junction), inhibited (sympathetic ganglia and intestine – leading to inhibition relaxation)
Noradrenaline	α_2	Inhibited
	β (?β_2)	Facilitated

From Lees, 1981. (14)