STUDY OF SOME METABOLIC EFFECTS OF THE BETA-ADRENERGIC BLOCKER (OXPRENOLOL)

THESIS

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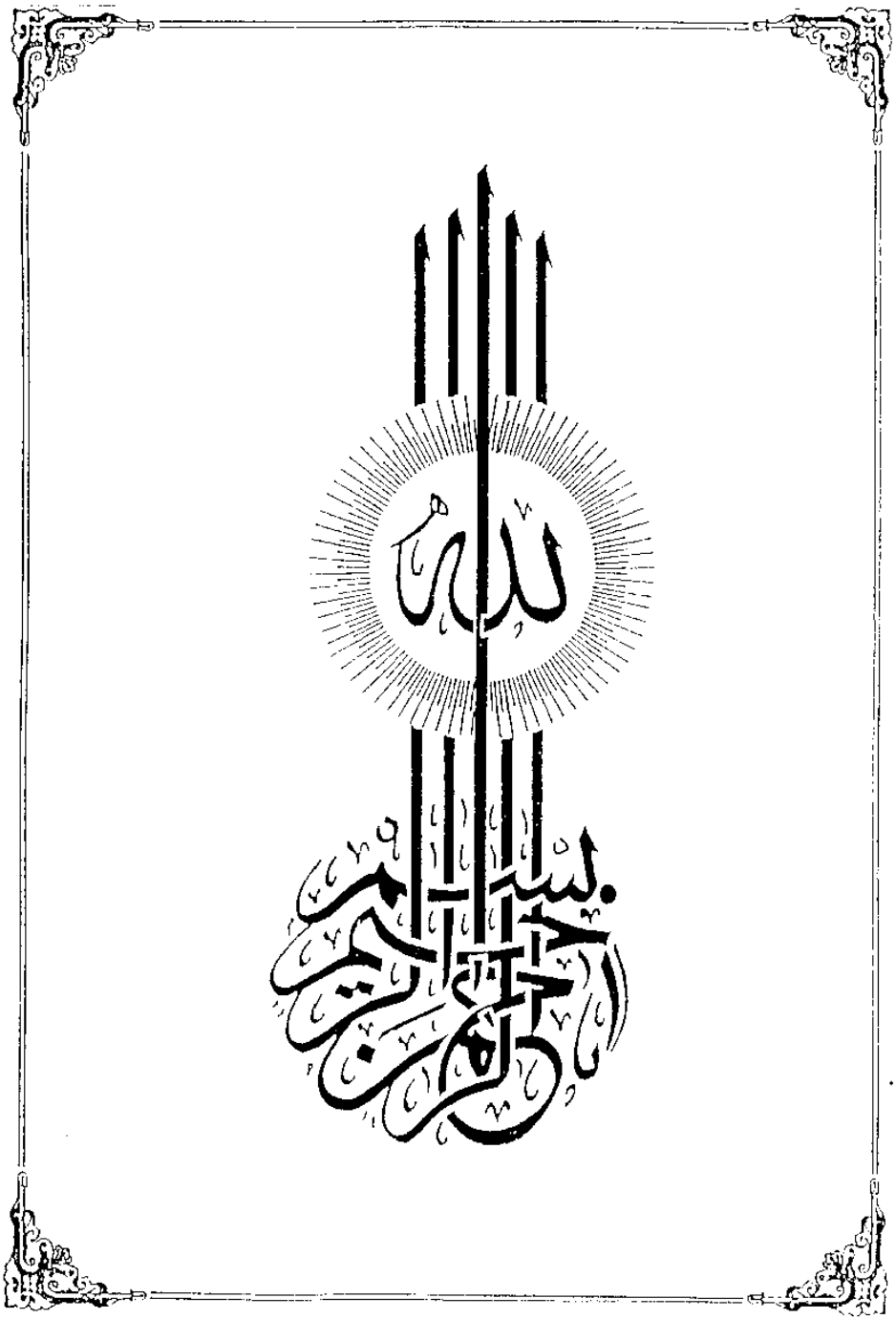

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CONTENTS

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INTRODUCTION

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"AUTONOMIC NERVOUS SYSTEM"

It is a large segment of the nervous system that operates at a subconcious level and controls many Functions of the internal organs, including the action of the heart, the movements of the gastrointestinal tract and the secretion of different glands. This system often operates by means of a visceral reflex arc. The autonomic impulses are transmitted to the body through two major subdivisions called the sympathetic and parasympathetic systems.

The sympathetic nerves originate between the first thoracic and the second lumbar segments. They begin in the sympathetic motor neurons of the interomediolateral horns of the spinal grey matter.

The sympathetic supply of the heart originates from the third to the sixth thoracic segments. Preganglionic sympathetic fibers reach the adrenal medulla without synapse all the way from the spinal cord to the gland, they end directly on special cells that secrete epirephrine and nor epinephrine (Arther C. Guyton, 1976).

Effects of stimulation of the sympathetic nervous system:

The adrenergic division discharges as a unit in emergency situations. For example, adrenergic discharge

relaxes accomedation and dilates the pupil, accelerates the heart rate and elevates blood pressure, it also lowers the threshold in the reticular formation, elevates the blood glucose and free fatty acids levels.

Cannon (1976), on the basis of effects like these, called the emergency-induced discharge of the adrenergic nervous system The "preparation for flight or fight".

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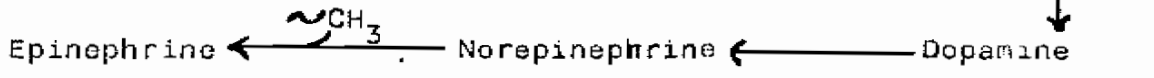
"SYMPATHETIC TRANSMITTER"

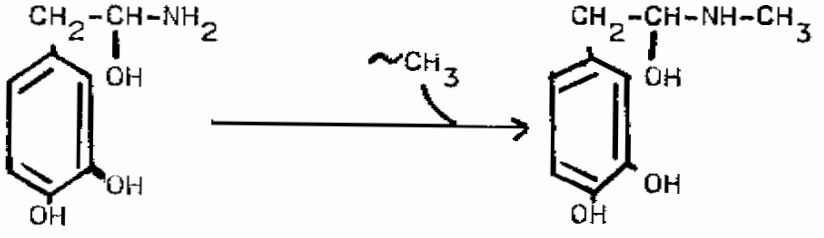
The majority of the postganglionic sympathetic nerve endings secrete norepinephrine, the chemical transmitter in the sympathetic nervous system, these fibers are said to be "adrenergic fibers". This hormone acts on different organs to cause the respective sympathetic effects, hence it is called (sympathetic mediator).

Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrnergic nerve fibers, but is completed inside the vesicles.

It is synthesized from the amino acid tyrosine → DOPA



The latter reaction occurs in the adrenal medulla to form Epinephrine.



Norepinephrine Epinephrine

Following secretion of nereptinephrine by the terminal nerve endings, it is removed from the secretory site in three different ways:

1. Re-uptake into the adrenergic nerve endings themselves by an active transport process accounting for removal of 50 - 80 % of secreted norepinephrine.
2. Diffusion away from the nerve endings into the surrounding body fluids and thence into the blood accounting for removal of most of the remainder of norepinephrine.
3. Destruction by enzymes to a slight extent "one of these enzymes is monoamine oxidase (MAO), which is found in the nerve endings themselves, and another is catecholamine -O- methyl transferase, which is present diffusely in all tissues".

Norepinephrine secreted by adrenergic nerve endings directly in tissues has a short life span (few seconds), in contrast to epinephrine and norepinephrine secreted by the adrenal medulla in blood, which act for a relatively long time (10 - 30 seconds).

This may be due to its rapid uptake and diffusion away from tissues in the former Case. The adrenal medulla secretes about 80 % epinephrine and 20 % norepinephrine (Gannong, 1977)

Stimulation of the adrenal medulla causes the release of hormones that have almost the same effects throughout the body as direct sympathetic stimulation, except that the effects are greatly prolonged, the only significant differences are caused by the epinephrine in the secretion, which, increase the rate of metabolism such as Glycogenolysis in liver and muscle and stimulates lipolysis and cardiac output to a great extent than is caused by direct sympathetic stimulation. Stress causes the "alarm reaction" of the sympathetic nervous system.

Metabolic actions of sympathetic transmitters (Catecholamines) (Vane et al.,(1960), Marley et al.,(1964) Acheson , et al., (1966) and Newman, et al., (1976) pointed out that:

Epinephrine and norepinephrine have actions on carbohydrate and lipid metabolism, epinephrine being more patent on the former and nonepinephrine on the latter.

1. On Carbohydrate metabolism:

Epinephrine raises the blood sugar occasionally to levels high enough to produce glucosuria, It also raises blood lactate level and increases oxygen consumption by about 30 % (Calorigenic action). The hyperglycaemia is due to stimulation of glycogenolysis and enhanced gluconeogenesis from lactate in the liver.

Adrenaline inhibits glucose - induced secretion of insulin from the beta-islet cells.

Adrenaline also causes the breakdown of glycogen to glucose through activation of adenylate cyclase with the formation of cyclic - adenosine monophosphate (Cyclic AMP). which stimulates Phosphorylase erzyme (The first enzyme in glycogenolysis) leading to the production of glucose-1-phosphate (G -1- P), that is changed into glucose - 6 - phosphate (G -6- P) and lastly to glucose, raising the blood sugar level; stimulation of glycogenolysis in muscle leads to increased blood lactate level due to absence of glucose - 6 - phosphatase in muscle. Adrenaline increases blood lactate and pyruvate, partly by promoting glycogenolysis in muscle , but also as the result of simulataneous increases in blood glucose and free fatty acid levels.

Noradrenaline which increases the plasma F F A levels does not raise the blood lactate because it does not cause hyperglycaemia.

2. <u>On Lipid metabolism</u>:

Adrenaline and noradrenaline activate a specific lipase in adipose tissue (fat cell lipase or Hormone - sensitive lipase), which breaksdown triacylglycerols into FFA and glycerol.

This lipolysis might be mediated by cyclic AMP; which is antagonized by insulin. In the liver some of the excess FFA is converted into ketone bodies. The catecholamines make available for the active tissues more oxidizable substrates, such as FFA, glycerol and ketone bodies and at the same time depress the oxidation of glucose. The lipolytic action of adrenaline is brief, that of noradrenaline is prolonged.

Biochemical actions and physiological responses:

The actions of catecholamines on the heart cannot be correlated with the activation of the adenylate cyclase cyclic AMP- phosphorylase system, since the inotropic action occurs before activation of phosphorylase. The principal metabolic fuel of the heart is lipid. Up to 80 % of the energy requirements of a heart stimulated by adrenaline is obtained from oxidation of lipid, mainly FFA released from cardiac lipids. Utilization of FFA reduces oxidation of carbohydrates.

The availability of the metabolic fuels, FFA and glucose, must be rapidly adjusted to the changing energy requirements of the body under various conditions of activity and stress.

The large fuel depots of triacylglycerole and glycogen can be drawn on in response to body demands. The sympathetic nervous system including the adrenal medulla can through release of its catecholamine mediators, speedly activate the enzymes which catalyze the breakdown of these stores of energy.

"Adrenergic Receptors"

Research experiments using different drugs called sympathomimetics) to mimic the action of norepinephrine on sympathetic effector organs have shown that there are at least two - and perhaps more - different types of adrenergic receptors.

I. Classification & Location:

Ahl quist (1948), proposed the existance of two types of adrenergic receptors from the fact that in some tissues, said to posses alpha-receptors, five catecholamines had one order of potency, whereas in other to poss beta-receptors, the order was quite different. The antisympathetic drugs then available, however,blocked the action of catecholamines only in these tissues with alpha-receptors, and another decade passed before Aliquist,s hypothesis was triumphntly vindicated by the discovery of specific beta-receptor Blocking drugs. Whereas no firm evidence has been obtained so far (reviewed by Furchgott,

1972) that there is more than one type of alpha-adrenoceptors, responses of tissues containing beta-receptors very quantitatively so much to various agenists and antagonists that is clear that the general group of beta - receptors" must be divided into subgroups.

Lands, et al.,(1967); Considered that there are only two subgroups: $Beta_1$ receptors in heart and intestine, and $Beta_2$ in other tissues and peripheral vasculature.

Bristow, et al., (1970) proposed that further variations have since been found between species and between different tissues in the same spices.

Charbon, et al.(1970) added that there is even difference between beta-receptors responsible for vasodilatation in different vascular regions of the same spieces.

Carlssone,(1977) stated that absolute organ separation of $beta_1$ and $beta_2$ - receptors as suggested by Lands (1967), inadquately reflects the true situation. The concept that each tissue possesses a single receptor type i.e.the heart possesses only B_1-receptors and other sites posses only B_2 receptors is false.It now appears that most tissues examined posses both B_1- & B_2 receptors,the relative proportions