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An Illustrative Study of Adrenergic and Adrenergic Receptor Blocking Agents in Autonomic Nervous System on Pharmacological Studies

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***Abstract*: Autonomic nervous system (ANS) was so named by Langley (1898) because of the fact that unlike the somatic nervous system of the skeletal muscles. It is independent of volitional control and thus enjoys some degree of autonomy. The sympathomimetic of adrenergic drugs mimic the responses obtained after stimulation of the sympathetic or adrenergic nerves, majority of these substances contain on intact or a partially substituted amino (-NH2) group and hence are called as sympathomimetic amines. Beta adrenergic blocking agents, a class of drugs also called beta blockers that block beta –adrenergic substance such as adrenaline (epinephrine) a key agent in the "sympathetic" portion of the autonomic (involuntary) nervous system. A wide variety of tissues undergo a change of functional state on exposure noradrenaline or adrenaline. Those molecular constituents of the effector cells of a tissue with which molecule of these catecholamine must first interact in order to produce a change of state or response of the tissue are the so called adrenoceptor (also commonly called adrenergic receptor). For convenience, we refer to noradrenaline, adrenaline and other agents which produce responses in tissue by interacting with adrenoceptors, as adrenergic agonists. An agent which specifically inhibits a response produced by an adrenergic agonist is referred to as adrenergic blocking agent or adrenergic antagonist.**

Key Words: Alpha adrenergic receptor, sympathetic nervous system, beta adrenergic receptor, catecholamine, acetylcholine, cyclic adenosine monophosphate, receptor antagonists, hypertension.

1. Introduction

Adrenergic receptor /or adrenoreceptors are a class of G protein–coupled receptor that are targets of the catecholamines, especially norepineprin (nor adrenaline) and epinephrine (adrenaline) many cells possess these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system. The sympathetic nervous system is responsible for fight–or flight response, which includes dilating the pupils, increase heart rate mobilizing energy, and diverting blood flow from non–essential organs to skeletal muscle.

Nor Epinephrine Receptors: Adrenergic Receptors; Nor epinephrine receptors are important clinically for three reasons: (1) their key role in physiology (e.g., cardiovascular, metabolic, renal); (2) the large number of drugs that target these receptors as agonists or antagonists; and (3) the contribution of these receptors in disease, including endocrine disorder. Information about physiologic actions and pharmacological derivative is available in many references. A few key disorders should be briefly mentioned [1]. Disorders of the endocrine pancreas, hyperthyroidism or hypothyroidism, and pheochromocytoma. Endocrine diseases of the pancreas, in particular, -cell disorders that are associated with hypoglycemia, lead to activation of the sympathetic nervous system and increases in circulating norepinephrine and epinephrine, the later primarily as a result of adrenal medullary stimulation. Hyper-thyroidism is associated with a number of signs and symptoms that suggest "hyperadrenergic state" e.g., tremor, tachycardia, arrhythmias [2]. pheocromocytomas, chromaffin cell tumors that are most commonly found in the adrenal medulla, produce high circulating levels of catecholamine, stimulation pf adrenergic receptors, and predictable effects of such stimulation in target cells. In addition to the direct activation of these receptors, the elevation of nor epinephrine can produce desensitization and down - regulation of adrenergic receptors. These feedback responses help buffer hypertension and other effects of chronic or episodic elevations in catecholamines, but also may contribute to the hypotension that can occur, especially in settings of receptor blockade or post operatively with removal of the catecholamine producing tumors [3]. Adrenergic receptors in endocrine and other disorders. The role of genetic variants of these receptors. In both their chemical structure and biological activities, adrenergics adrenergic blocking agents constitute an extremely varied group of drugs whose clinical utility includes prescription drugs to treat life threatening conditions such as asthma and hypertension as well as non-prescription medication for minor ailments such as the common cold [4]. This extensive group of drugs includes synthetic agents as well as chemicals derived from natural products that have been used in traditional medicines for centuries. Many adrenergic drugs are among the most commonly prescribed medications in the United States, including bronchodilators, such as albuterol for use in treating asthma and hypertensives, such as atenolol and doxazosin. Nonprescription adrenergic drugs include such widely used nasal decongestants pseudoephedrine and naphazoline. Most of these varied drugs exert their therapeutic effect through action on adrenoreceptor, G-protein-coupled cell surface receptors for the neurotransmitter norepinephrine, and the adrenal hormone epinephrine subdivided.

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Identification of subclasses of adrenoreceptor has been greatly aided by the tools of molecular biology and to date six distinct α –adrenoreceptors [5].

2. Materials and Methods

Alpha adrenergic receptors are two types such as alpha$_1$ and alpha$_2$, with three sub types each. Alpha$_1$ adrenergic receptors (post synaptic) are predominantly in the vascular smooth muscles. Activated of these receptors which are excitatory in nature increase the intracellular concentration of calcium by activation of phospholipase C in the cell membrane via stimulatory G-protein [6]. The phospholipase C then hydrolyses membrane bound phosphoinositides with the generation of two second messengers diacylglycerol and inositol triphosphate. This results in an increase in the intracellular ca^{++} which accounts for the vasoconstrictor effect. Alpha$_2$ α_2) adrenergic receptors are found both in effector tissues (post synaptic) and on the neuronal endings (presynaptic) where they are autoreceptors. Activation of the presynaptic α_2 receptors by agents acting through the inhibitory G protein (G_1) inhibits adenylyl cyclase and reduces the intracellular concentration of cyclic AMP [7]. These receptors activate G-protein gated K^{++} channels. The presynaptic α_2 receptor agonists produce inhibitory effect, thus, activation of the α_2 receptors in the adrenergic nerves inhibits NA release [8].

Table-1
Distribution and responses of adrenergic receptors

Tissue	Response
Predominantly alpha receptors (a) Medulla oblongata (α_2)	Reduction of BP and heart rate
(b) Blood vessels: (α_1) skin and mucosa cerebral	Constriction Constriction(slight)
(c) Skin: pilomotor muscle (α_1) Apocrine sweat gland (Renin release)	Contraction Secretion increases
(d) Radial muscle of iris (α_1)	Constriction (miosis)
(e) Salivary glands except parotids	Thick, viscous secretion

The activation of the postsynaptic vascular α_2 receptors however, causes release of endothelium derived relaxing factor (EDRFNO) which brings about vasodilation. Activation of venous α_2 receptors, on the other hand, causes veno constriction. This neuromodulatory system appears to play an important role in the control of sympathetic tone. Activation of the post-synaptic α_2 receptors in the GI tract acts by inhibiting voltage sensitive calcium channels leading to relaxation [9]. Alpha$_2$ adrenergic receptor are also present at the post–junctional or non junctional sites in several tissues such as the brain. Activation of post–junctional alpha$_2$ receptors in the brain by clonidine causes the anti-hypertensive effect. The presence of α receptors has been also demonstrated on human leukocytes and platelets [10]. The predominant receptor in various organ and the usual responses to their stimulation are given in the table. These responses in isolated tissues may differ from those in the whole animal owing to the presence of compensatory reflex activity [11]. The initial condition of the tissue may also determine the result out responses.

Table-2
Tissue and Response

Tissue	Response
Predominantly beta receptors (a) Heart (β_1, α_1) (i) S-A node - β_1 (ii) Atria - β_1 (iii) A-V node - β_1 (iv) Ventricles - β_1	Increased heart rate (positive chronotropic action) Increased contraction (positive ionotropic action) and faster conduction Increased contractility and conductivity Increased automaticity (positive chronotropic action)
(b)Bronchial muscle - β2	Relaxation
(c) Skeletal muscle change -β_2	Changes in contractility

Table-3
Both alpha and Beta receptors

G.I tract: Motility and tone (α_2, β_2) Sphincters(α_1) Pancreas: Alpha$_2$ Beta$_2$	Decreased Contraction Inhibiting insulin release Stimulation of insulin release
Urinary bladder: Trigone – α_1 A Detrusor - β_2	 Contraction Relaxation
Blood vessels: Coronary-α, β_2 Pulmonary - α, β_2 Abdominal viscera - α, β_2 Renal- α, β_2 Skeletal muscle α, β_2	 Constriction; dilatation Constriction; dilatation Constriction(mainly);dilatation Constriction; dilatation Constriction; dilatation
Adipocyte - α_2 β_3 Liver - α - β_2	Inhibit lipolysis Lipolysis Glycogenolysis, Neoglucogenesis & Inhibition of glycogen synthetase
Leukocyte (human) - β_2 Platelet (human)- β2	Inhibits chemotaxis and lysosomia enzyme release Platelet aggregation

Adrenergic and adrenergic blocking drugs:

1. Adrenergic drugs used for rising blood pressure: Nor adrenaline,Metaraminol,Phenylephirine.
2. Those used for their iontic action on the heart: Dopamine, Dobutamine, Isoprenaline.
3. Those used as central stimulant: Amphitamine, Dextro Amphetamine and Methyl phenidate.
4. Those used smooth muscle relaxants:
   a) Non selective beta stimulant such as Adrenaline and Isoprenaline.
   b) Selective β_2 stimulants. Salbutamol and Terbutaline.

5. Those used in allergic reaction: Adrenaline, Ephedrine.
6. Those used for local vasoconstrictor effect: Adrenaline, Naphazoline, phenylephrine, xylometazoline.
7. Those used for suppressing the appetide: Fenfluramine, Phenteramine [12].

Table-4
Drugs acting on adrenergic receptor subtypes

Agonist/ Antagonist	Alpha 1	Alpha 2	Beta 1	Beta 2
Agonists	Phenylephirine	Agonists	Phenylephirine	Agonists
Antagonists	Prazosin		Antagonists	Prazosin
Location of receptors	Postsynaptic (vessels, Glands and smooth Muscle)	Presynaptic Postsynaptic (vessels and brain tissue)	Location of receptors	Postsynaptic (vessels, Glands and smooth Muscle)
Mechanism of action	Alteration of cellular calcium ionfluxes	Inhibition of adenylyl cyclase	Stimulation of adenylyl cyclase	Stimulation of adenylyl cyclise

Criteria of Neuro humoral transmitter:

- Should be present in presynaptic neurone along with enzyme synthesizing.
- Should be released in the medium following nerve stimulation.
- Its application should produce responses identical to nerve stimulation.
- Its effect should be antogonised or potentiated by other agents.

Sites of cholinergic transmission:

Recent biochemical and immunohistochemical studies have shown that the opioid peptides, enkephalins, occur in nerve terminals and cell bodies in mammalian sympathetic ganglia 1-3. Opiates and enkephalins are thought to inhibit synaptic transmission in the peripheral nervous tissues as well as in the central nervous system 4-12 [13]. The mechanism of opiate actions, however, are not entirely clear, both pre and post synaptic sites of action have been proposed 7-9, 11, 12. As acetylcholine is known to be major neurotransmitter in the autonomic ganglia and as the mechanism of synaptic transmission well clarified 13, analysis of the peptide action could be more easily but equally usefully carried out in the peripheral synapses than in central synapses. We now report that enkephalins presynaptically inhibit cholinergic transmission in sympathetic ganglia.

3. Results and Discussion

The influence of antagonist muscle control strategies on the isometric frequency response of the cat's ankle joint [14]. This study investigated the effect of various strategies to control the interaction between agonist and antagonist muscle on the frequency response of the isometric cat ankle joint actuated by the tibialis anterior(TA) and soleus (SOL) muscle .Some strategies were based on the physiological need for increasing joint stability during forceful contraction with these strategies, the proportion rate of physiological need for increasing joint stability during forceful contractions with these strategies, the proportion rate of physiologic antagonist activity was termed antagonist gain [15]. Other strategies were based on the electrical stimulation literature, which advocates contraction at low force level. Since in this study the compounds that showed alpha adrenergic receptor blocking activity were all developed on the basic arylalkylamine pattern differing in regard to the nature and position of the substituent groups any generalization made will be pertinent only to such compounds. Alpha adrenergic receptor blocking agents are characterized by a nonspecific nature of their chemical structures, and this lack of specificity precludes any generalized consideration. β - Adrenoceptor antagonists (β-blockers) are one of the most widely used classes of drugs in clinical practice and are currently used in the management of hypertension, ischaemic heart disease, heart failure anxiety, tremor migraine and glaucoma [16]. This study suggests that many ligands previously considered having β_1-selectivity, for example metoprolol and atenolol have poor β_1 / β_2 selectivity, while others that are often prescribed for cardiovascular disorders for example, carvedilol, sotalol and timolol actually have higher affinities for the β_2 adrenoceptor [17]. Although the affinity of great many β - adrenergic ligands has been assessed over the years, direct comparisons are often difficult to interpret as studies have been conducted in different tissues, from different species and by different methods. Thus although in the clinical setting β blockers are primarily used for their β_1 – antagonist effect, the majority actually appear to have rather poor β_1/β_2 selectivity. However, despite this, β-blockers have been and continue to be a highly effective treatment for many cardiovascular disorders. The effectiveness of the drugs in man obviously depends on more than just receptor affinity 18. The pharmacokinetic profile of the drugs, the absorption, metabolism, tissue distribution and elimination of the drugs, as well as their longevity of action at the given receptors, also are important.

4. Conclusion

Discontinuing beta blockers immediately after vascular surgery may increase the risk of post-operative cardiovascular morbidity and mortality. Although selective β_1 antagonism is the goal of most β - blocker treatment regimes, the majority of clinically used β - blockers have little selectivity for the human β_1 over the human β_2 adrenoceptor in intact living cells. Clearly, as more β_1-adrenoceptor selective antagonists do exist than those currently clinically available (e.g. CGP 20712A), there is considerable potential for developing more selective β-antagonists for clinical use and thereby reducing the side effect profile of β blockers. Many 'β- blockers' are not neutral antagonists, but have some antagonist, but have some agonist and inverse agonist actions of their own at the different β-adrenoceptors .The contribution of this to their overall clinical effects is so far unknown. However, the clinical benefit of β-blockers in heart failure does not appear to be a class effect, nor is it completely explained by β_1- antagonism. The agonist and inverse agonist effects of the different β-blockers may therefore explain some of the differences between drugs and their mode

of action in condition where β_1 - antagonism does not seem to be whole explanation.

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