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Cardiovascular Medications, Beta-Blockers and their Effect on Cells

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Introduction

Cardiovascular disease is the leading cause of death in the United States. Approximately 2200 people die from heart disease and stroke.[1] Many families have relatives who suffer from cardiovascular disease. People are relying on medications as a way of slowing down the effect of cardiovascular disease. The Department of Health and Human Services has developed an initiative designed to prevent heart attacks and strokes by the end of 2016. The "Million Hearts Initiative", began in September 2011. The goal of this initiative is to empower Americans to make healthy choices and improve care for individuals who my need treatment.[2] Treatment for cardiovascular disease consists of a wide array of medications. The unit examines the utilization of beta-blockers as a method of treating cardiovascular disease. The unit is designed for students taking a biology/life science course in high school.

Overview

The method of introducing cardiovascular medications into the body will vary. Drug delivery to the cardiovascular system is unique because of the anatomy and physiology of the vascular system. The vascular system supplies blood and nutrients to all organs of the body.[3] Delivery of drugs to the cardiovascular system is approached on three levels: routes of drug delivery, formulation, and application to various diseases. Formulation for drug delivery into the cardiovascular system range from controlled release preparations to the delivery of proteins and peptides. Biomedical engineering research scientists are developing cell selective target drugs. Nanotechnology is another way of improving the systematic administration of drugs for cardiovascular disorders. Cell-selective targeted drug delivery is another way to maximize the effectiveness of a drug and limit the pharmacological activity to relevant tissues thereby limiting the exposure to other cells.[4] Many different categories of drugs are used to treat cardiovascular disease. The unit will concentrate on beta-blockers drugs. The history of beta-blockers and how they affect the cell will be examined in this unit.

Rationale

The number of individuals suffering from heart related illness has increased. Many people take prescriptive heart medications on a daily basis. The statistics indicate an increase in heart disease in African American and Hispanic communities. Dietary and life style issues have caused a surge in the number of individuals suffering from heart related problems. Many students have parents and family members that suffer from heart disease and other related illness. They observe their parents taking various forms of medications. The method of introducing the medicine into the body varies. In some cases they even help to administer the drug to their parents.

I want my students to learn about how heart medications are delivered into the body and how they affect the cells. Drugs work because of their action on cells in the body. It is important for students to understand the function of the cell and how form is related to function. The state of Pennsylvania has adopted a new test called the "Keystone Exam". Many assessment anchors address the role of prokaryotic and eukaryotic cells in the body. Students are required to describe the relationship between structures and function at various levels of organization. I will have the opportunity to identify specific cells and examine the role played by atoms, molecules, and macromolecules. It is incumbent on me to make concepts relevant to my students because they will learn how the molecule works inside the body.

Background

Classification of heart medications

Many different types of medications are used to treat heart disease. The medicines are divided into ten basic groups.[5]

1. Anticoagulants: Anticoagulants also called blood thinners decrease clotting. They do not thin your blood; however they can prevent the formation of blood clots inside of your blood vessels.
2. Antiplatelet Agents: Antiplatelet agents prevent blood platelets from forming aggregates (or clumps) inside of your blood vessels. Many people take aspirin on a daily basis because it is an antiplatelet agent.
3. Angiotensin-Converting Enzyme (ACE) Inhibitors: Angiotensin-Converting Enzyme (ACE) inhibitors cause the blood vessels to expand allowing the blood to flow easier through the vessels. The heart is more efficient when ACE inhibitors are taken. They decrease the resistance of vessels to flow—and therefore lower blood pressure—by lowering the levels of angiotensin-II. Angiotensin is a protein that is found in the body. Angiotensin I is converted into angiotensin II by removing the c-terminals on the molecule. This happens inside of your kidney. When the blood volume is low specialized cells inside of your kidney secrete an enzyme called renin directly into your blood. Renin cleaves an inactive peptide called angiotensinogen converting it to angiotensin I. Angiotensin I is converted into angiotensin II by an enzyme called angiotensin converting enzyme (ACE). Angiotensin II increases the risk of a heart attack and stroke because it elevates your blood pressure. Angiotensin promotes the stimulation of Gp proteins found in smooth muscle cells. The Gp protein activates heart contraction by IP3 dependent

mechanism. ACE inhibitors are used to treat hypertension and heart failure because they prevent the activation of the Gp protein inside vascular muscle cells.[6]

4. Angiotensin II Receptor Blockers (Inhibitors): Angiotensin II Receptor Blockers (inhibitors) prevent angiotensin II from having any effect on the heart and blood vessels. Inhibitors lower the blood pressure of individuals taking this type of drug.
5. Beta-Blockers: Beta-blockers, also called Beta-Adrenergic Blocking Agents, decrease the heart rate and cardiac output. They are used to lower blood pressure and treat patients suffering from irregular heartbeats. Beta-blockers are given to individuals who have experienced previous heart attacks.
6. Calcium Channel Blockers: Calcium Blockers interrupt the movement of calcium into the cells of the heart and blood vessels. Calcium blockers are used to treat high blood pressure, chest pain, and abnormal heart rhythms.[7]
7. Diuretics: Diuretics (water pills) cause the body to get rid of sodium through urination. Diuretics decrease the amount of fluid in the body. Fluid tends to accumulate in areas of the body such as the ankles and legs. The workload of the heart decreases when excess fluid is eliminated. Diuretics are used to help lower the blood pressure and reduce the swelling caused by the buildup of excess fluid in the body. The swelling in the body caused by the retention of fluid is called edema.[8]
8. Vasodilators: Vasodilators (nitrates) relax the blood vessels thereby causing an increase in the blood supply. More oxygen is delivered to the heart allowing the heart to become more efficient. The workload of the heart is decreased when patients take these types of drugs. Vasodilators are usually given to patients who cannot tolerate ACE inhibitors. Vasodilators can be administered in the form of a pill, chewable tablet or a topical cream. They are mainly used to ease chest pain (angina).[9]
9. Digitalis Preparations: Digitalis increases the force of the heart's contraction. Digitalis is used on patients who don't respond to ACE inhibitors and diuretics. Digitalis preparations are given to patients who suffer from irregular heartbeats and heart failure.
10. Statins: The final category of heart medications is Statins. Statins are used to lower cholesterol levels inside the body. Statins work on several parts of the body such as the liver, intestines. The body produces two types of cholesterol. Good cholesterol (HDL) and bad cholesterol (LDL). Statins interrupt the formation of bad cholesterol from circulating in the blood.[10]

Historical Facts

Receptors are molecules found on the surface of a cell. Receptors recognize and bind to specific molecules. Many types of receptors are found in the human body. Receptors are important because they aid in the passing of information from one cell to another. Adrenergic is a term associated with the activation of adrenaline (epinephrine) and or noradrenaline in the body. Adrenergic receptors are proteins that are sensitized to particular chemical compounds. Adrenergic proteins can stimulate many responses in the body. They can trigger muscle contraction and they are involved in certain secretions that modulate blood pressure. Adrenergic receptors are divided into two major types: alpha and beta-adrenergic receptors along with two subgroups. The concept of using adrenergic receptors has been around for a long period of time. It can be traced back to 1905. Langley postulated that a cell might make motor or inhibitory receptive substances. The effect of a new impulse depends upon the proportion of the two kinds of receptive substances affected by the impulse.[11] The following year Sir Henry Dale showed that you could use ergot to block excitatory actions of adrenaline. Some of the alkaloids found in ergot are used as medicines. Ergonovine is an example of one of the alkaloids used medicinally to stop a person from hemorrhaging. It also causes contractions in the uterus. Midwives used ergot to stop postpartum uterine bleeding during the 17th Century. Women used it to speed up labor.[12]

In 1910 Barger and Dale wrote a paper together describing the structural activity relationships that exist among sympathomimetic amines. The most notable feature was "the more or less strict" localization of their action to cells. They concluded that there must be something in these specific cells or connected with them that have a strong affinity for sympathomimetic amines. Specific chemical receptors inside of the cells are sensitive to amines.[13]

In 1933 Cannon and Rosenblueth developed an idea that a specific transmitter substance is released by sympathetic nerve endings. The transmitter combined with either and excitatory (E) or inhibitory (I) substance form sympathin (E) and sympathin (I). They could now act on the tissues or be released into the blood in different amounts. In 1948 Dr. R. P. Ahlquist published a paper describing the effect of six different sympathetic simulating drugs on adrenergic responses. He referred to them as alpha and beta-receptors. A majority of the alpha effects were excitatory. Some of the effects include stimulation of the uterus, nictitating membrane, and ureter and dilator pupillae. The only inhibitory action was intestinal relaxation.[14] In the intestine Adrenaline (epinephrine) is the most potent neurotransmitter followed by noradrenaline (norepinephrine). A majority of the beta "adrenotropic receptors" are associated with inhibitory actions such as vasodilation, inhibition of the uterine and bronchial smooth muscle. The only beta excitatory action was myocardial stimulation. Myocardial stimulation results when you have a difference in the electric potential across the cell membrane.

Ahlquist realized that receptors could either be excitatory or inhibitory. He concluded that one receptor type was not limited to a specific excitatory or inhibitory effect. Isoprenaline is the most active beta-receptor followed by adrenaline. Noradrenaline was the least effective beta-receptor. The editor of the Journal of Pharmacology and Therapeutics rejected Ahlquist's paper because it challenged the sympathin theory developed by Cannon and Rosenblueth. Since then the receptors have been divided into the following groups, $alpha_{,1}$ $alpha_2$, $beta_1$ and $beta_{2\,15}$.

The Lilly laboratories were actively involved in screening several compounds that would have a relaxant effect on pilocarpine contracted tracheal chains. Tracheal chain preparation is a technique used for recording the constriction and dilation of the trachea when exposed to certain types of drugs. The trachea muscle of guinea pigs and rats are in these preparations because they conduct good smooth muscle reactions. Smooth muscle tissues line our blood vessels and organs. They control the flow of blood through blood vessels Compound 20522 dichloroisoprenaline (DCI) blocked the relaxant effect of adrenaline. DCI inhibited bronchodilator, vasodilator, and inhibitory actions of adrenaline. In 1958 Moran and Perkins reported the blockade of the cardiac stimulant effects of adrenaline by DCI. They concluded that the selective blockade of most inhibitory functions and the lack of blockade of vasoconstriction combined with the present demonstration of blockade by DCI of cardiac positive isotropic and chronotropic effects of adrenotropic stimuli support the postulate of Ahlquist.[16]

James W. Black was interested in coronary artery disease. He thought that there was a better way of treating coronary artery disease. Black was interested in developing ways of reducing oxygen consumption instead of trying to increase the flow of oxygen in the coronary artery. He stated that there are two differentiated sympathetic receptors. Alpha-receptors are associated with excitatory effects on smooth muscle receptors and beta-receptors are associated with inhibitory effects on smooth muscle and cardiac muscle. He concluded that all of the known adrenolytic agents acted on alpha-receptors. The major contribution made by Black was an appreciation of the possible clinical value of developing compounds to inhibit the sympathetic nervous system on the heart. Black persuaded the Imperial Chemical Industries (ICI) to allow him to lead a team of

scientists and translate the idea into the real world.[17] Black invented two beta-blocker drugs (Propranol and Pronethalol) that are widely used by heart patients. Propranol was considered a great invention and Black was awarded the Nobel Prize for medicine in 1988.

Role of Beta-Blockers

Beta-blockers work by blocking the transmission of certain nerve impulses. Nerves release chemical substances called neurotransmitters when they are stimulated. Noradrenaline is an example of a neurotransmitter found at the end of several nerve cells in our body. The chemical stimulates the beta-adrenergic receptors on the cell. Receptors are tiny structures found on the surface of cells. Receptors are found on the cells that make up the heart, brain, and blood vessels.[18] Many things happen whenever receptors are stimulated. Nerve impulses leading to the heart stimulate beta-adrenergic receptors found in heart cells causing an increase in the heart rate. Beta-adrenergic receptors are also stimulated by adrenaline. Adrenaline is a hormone made in the adrenal gland. The hormone is circulated throughout the body via the bloodstream. A significant amount of adrenaline is released into the body whenever a person is frightened or startled. A good example is the "fight or flight" response. Beta-blocker drugs sit on beta-adrenergic receptors in the heart. They block the receptor from being stimulated. When beta-adrenergic receptors in the heart are blocked the rate and force of the heartbeat is reduced. This causes the blood pressure to drop and the heartbeat slows down.[19]

Classification of Beta Blocking Drugs

Beta-adrenergic receptors have both isotropic and chronotrophic effects. When agonists bind to them they increase the force of concentration and reduce the time to peak force. The relation time is reduced while the heart speeds up. The positive inotropic action differs from the beta-mediated relaxation of the vascular smooth muscle. Metabolic changes include the stimulation of glycogenolysis (breakdown of glycogen) and lipolysis (breakdown of lipids).[20]

Beta blocking drugs are divided into two groups and each of these groups is divided into smaller subgroups. Beta-blocking drugs can be nonselective or have a selective action on one type of beta-receptor. Beta-blockers can also have alpha-receptor blocking properties. The subgroups are divided into various groups according to the presence or absence of intrinsic sympathomimetic activity (ISA) and membrane activity.[21] Specialized structures located on the cell and inside of the cell called beta adrenoceptors allow it to interact with epinephrine and norepinephrine and other beta agonists. A complementary structural relationship develops between the drug and the beta adrenoceptors. The binding of the drug to the adrenoceptors produces a change in the receptor and initiates the movement of ions.[22] The movement of ions activates the release or production of energy. Isoproterenol is one of the most potent synthetic drugs. The structure of the molecule has a great deal to do with the effectiveness of the drug. All of the effective antagonists for beta-receptors have a ring structure attached to the side chain of alanine.

Antiarrhythmic Drugs

Antiarrhythmic drugs should be used cautiously. Physicians have to make a careful assessment of the risk versus the benefits of using these drugs. Drug interactions are common in patients taking these kinds of drugs. Patients suffer depressed ventricular functions and have a greater risk of drug-induced proarrhythmia (irregular heartbeat). Many drugs have negative inotropic effects and tend to aggravate heart failure.[23]

Beta-blockers are the first line of therapy for individuals suffering from arrhythmias. They have antiarrhythmic effects and are efficient in increasing the life expectancy for individuals suffering from arrhythmia. Beta-blockers have reduced the number of sudden deaths due to heart failure. Beta-adrenergic blockers alleviate the symptoms of palpitations associated with premature ventricular contractions. Many ventricular arrhythmias are aggravated by sympathetic stimulation. Beta-adrenergic blockers are effective in reducing the frequency of many ventricular arrhythmias and sudden death in patients suffering from this condition. Sympathetic stimulation can reverse the time of electrophysiological effects for amiodarone and other antiarrhythmic drugs.[24]

Intrinsic Sympathomimetic Activity (ISA)

Beta-blockers with ISA exert a low level of stimulation at the adrenergic receptors while simultaneously blocking the endogenous catecholamine such as epinephrine and norepinephrine from binding to the receptor. This characteristic is a result of the direct substation of the ring system with polar or electron withdrawing groups. Polar substitution of the aromatic ring of aryl ozypropanolamines has been shown to increase sympathomimetic activity. Substitution of the terminal nitrogen in N-aryloxyethyl in place of more usual groupings can eliminate intrinsic activity; however amine substituents are more potent both as agonists and antagonists than their parent substances. They have a high affinity for the beta-receptor than either of the parent substances.[25]

Adrenoceptors blockers

Blockade of Exogenous Stimulation

Beta-adrenoceptors blocking drugs are competitive inhibitors (antagonists) at the beta-adrenergic receptor. If you increase isoproterenol it will overcome the block because it is a stimulating drug called an agonist. Competition exists between the agonist and the antagonist. The net effect on the receptor is proportional to the local concentration of the agonist and the antagonist. A complete beta blockade doesn't exist in terms of an exogenous stimulus such as in isoproterenol. An increase in the concentration of the antagonists can be overcome by increasing the concentration of the antagonist. A large disparity exists between beta blocking drugs and their ability to inhibit isoproterenol. The reason for the differences appears as a result of the beta-1 and beta-2 receptors in the atria.[26]

Response to a single dose of isoproterenol is not a good way of assessing a beta blockade. The response of individuals taking single doses varies widely from one individual to another. A number of factors are involved whenever you compare individuals taking the same drug. You have to examine all pre-existing medical conditions, the age of the patient, lifestyle, method of delivery, weight, and sex of the individual. The response to a previously adequate dose of isoproterenol is abolished completely for a prolonged period of time after taking an oral dose of a beta-blocking drug.[27] It is difficult to assess the degree of change for a beta-receptor antagonism once the drug concentration alters. In order to obtain a dose response curve multiple doses of isoproterenol are required. The dose response curve can be obtained by using intramuscular injections or by continuous infusions of isoproterenol. Continuous infusions provide more exposure to the unpleasant effects of isoproterenol.[28]

Blockage of Endogenous Stimulation

A test is used to determine the actual amount of endogenous sympathetic activity. The test for beta blocking

is more sensitive when there is a higher degree of endogenous sympathetic activity. When a person is at rest or lying down the vagal tone is in control. During this time the sympathetic tone is low. The parasympathetic nervous system is responsible for all "rest and digest", functions. The vagal tone is influenced by the parasympathetic nervous system. In the resting state the heart rate will fluctuate with the breathing cycle.[29] When a person stands the sympathetic tone slightly increases. The low levels of sympathetic activity make it possible to demonstrate a dose-response relationship with a beta antagonist that does not possess a partial agonist activity.[30]

Monotherapy vs. Combination Therapy

Hypertension is a heterogeneous disease, and the same drug cannot normalize the blood pressure in every patient. The physician will choose among the different classes of drugs (antihypertensive agents, diuretics, beta blockers, alpha$_1$ blockers, calcium antagonists, blockers of renin-angiotensin system, angiotensin-converting enzyme, ACE inhibitors, angiotensin II antagonists and AT$_1$ receptor antagonists).[31] Monotherapy combined with another drug from one of the groups previously mentioned can control blood pressure in approximately one half of the patients suffering from hypertension. Patients who do not respond to this treatment are given dosage adjustments. This approach is not widely used because most antihypertensive drugs show a close-dependent increase for having side effects.

AT$_1$ receptor antagonists have a positive advantage because they are considered a well-tolerated drug in most patients. It is possible to achieve full inhibition of the renin-angiotensin system without causing more side effects.[32] Even when optimal blockade of AT$_1$ receptors are used they did not normalize the blood pressure in patients with a non-renin-dependent form of hypertension. Physicians will switch to another class of antihypertensive agents if a patient does not respond effectively to one type of drug.[33] This approach is commonly referred to as Sequential Monotherapy. This type of therapy may require a patient to receive one drug for a specific period of time. Patients will be given another drug for the exact same period of time. This process is repeated again and again using a different drug. For example, they will be given a diuretic for four weeks, a beta-blocker, a calcium antagonist and an ACE inhibitor for the exact same time period. During the initial phase of the treatment blood pressure normalized in approximately 39% of the patients. Upon completion the drug rotation cycle normalization of the blood pressure occurred in 73% of the patients. The results indicated that it was possible to control blood pressure in most hypertension patients. However this form of treating hypertension tends to discourage patients because it is time consuming and patients tend to stop the procedure.[34]

Another approach used to improve antihypertension efficiency is combining drugs that act on different mechanisms in the body. Multiple effects on the cardiovascular system increase the probability of normalizing blood pressure. Antihypertensive efficiency caused by a given drug may weaken compensatory and renal responses commonly found when administering another type of antihypertensive drug. Diuretics increase urinary sodium excretion and trigger the release of renin from justaglomerular cells.

Ace Inhibitors and the kidney

Ace inhibitors can modulate intraglomerular pressure because the angiotensin-II receptors found in the proximal part of the renal afferent arterioles help control intraglomerular filtration pressure.[35]

Physicians encounter patients taking drugs to control blood pressure have an increase in serum creatinine

concentration and some patients even develop a condition known as hyperkalaemia.[36] Hyperkalemia is a medical term used to describe a condition when the electrolyte level of potassium in the blood is higher than normal. Your blood potassium is normally 3.6 to 5.2 millimoles per liter (mmol/L). Medical attention is required whenever your potassium level is higher than 7 mmol/L. Hyperkalemia is caused by kidney failure, alcoholism, heavy drug use, ACE Inhibitors, and Addison's disease. Addison's disease is widely known because President Kennedy suffered from this disease. Hyperkalemia can cause irregular heart rhythms, muscle fatigue, paralysis, and nausea in patients. Kidney function can be prolonged when certain medications are reduced. Decreasing the dose of antihypertensive medications can reduce the level of serum creatinine concentration, this will cause the blood pressure to increase and the serum creatinine levels will return to their original baseline. This approach is highly discouraged because it is not optimal for long-term preservation of renal function.[37]

Small and non-progressive increases in serum creatinine concentration provide better blood pressure control and do not cause any structural damage to the kidney. It is favorable because it tends to lower intraglomerular pressure. It is not in the best interest of patients who suffer from hyperkalaemia to stop taking angiotensin-converting enzyme (ACE) and angiotensin receptor blocker (ARB) therapy. It is in the best interest of the patient to minimize this complication given the potential cardiovascular benefits of ACE inhibitors and ARB therapy. By taking several precautions a majority of patients at risk for hyperkalaemia can be treated successfully rather than being labeled as intolerant to these drugs.[38]

The control of serum creatinine concentration along with regulating blood pressure is the major problem for patients who suffer from chronic renal failure. Loss of renal mass leads to a disruption in the autoregulatory ability of the renal vasculature. The intraglomerular pressure begins to change as a result of a change in the systemic arterial pressure.[39] In some patients this problem is so severe that they develop a pressure-passive vasculature. This occurs whenever a change in the mean arterial pressure is matched by a proportional change in intraglomerular pressure.[40] These changes explain why hypertensive chronic renal failure patients suffer from increase serum creatinine concentrations when the blood pressure is lowered. Renal function will either improve or resolve with long-term blood pressure control. The long-term renal outcome is still better in patients who have their blood pressure under control even if the renal functions are slightly reduced.[41]

Black patients with hypertension

Ace inhibitors are not as effective in black patients when compared to white patients. Diuretic therapy is often required in order to achieve a benefit. White patients had a mean seated blood pressure decrease of 14.7/10.7 mmHg after taking the drug captopril. The blood pressure in black patients fell by 9.1/7.9 mmHg after using the same drug. Blood pressure decreased about the same for both groups when the hydrochlorothiazide was given. Both of the groups were given the same dosage. In the case of enalapril, hydrochlorothiazide addition rendered the drug equally effective in black and white patients. In the case of lisinopril there were similar racial differences in the response. Even with the addition of hydrochlorothiazide blood pressure decrease was greater in white patients when compared to black patients.[42]

Black patients are thought to have low renin hypertension and this is the probably the reason why they respond less to ACE inhibitors. A low salt diet and/or diuretic therapy should increase renin levels and make patients more susceptible to ACE inhibitor therapy.[43] The use of ACE inhibitors is the first line therapy. ACE inhibitors are used when patients suffer from ventricular failure, peak physical and mental activity are required combined with lipid profile, borderline glucose tolerance, presence of diabetes mellitus along with

nephropathy, peripheral vascular disease, and hypertension is predominately systolic along with contraindications to beta-blockade therapy.[44]

Beta blockade therapy is favored when patients have ischemic heart disease, angina, and the post-infarct state unaccompanied by left ventricular dilation, co-exiting anxiety, pre-existing dry cough and pregnant hypertensive patients. In this case neither type of agent is suited for first line therapy of black hypertensive patients.

Quality of life

The quality of life is more is affected when patients use beta-blocking drugs. Patients with mild to moderate blood pressure are usually asymptomatic. These patients tend to prefer ACE inhibitor therapy. Beta-blockers have several adverse effects. Patients suffer from vivid dreams, impaired memory, sexual dysfunction and lethargy. Although these characteristics are not life threatening it is unpleasant for most patients. Patients prefer ACE inhibitor drug therapy because the side effects are not quite as unpleasant as Beta-blocker therapy.[45]

Types of Beta Blocker Drugs

Cardioselective beta blockers (more likely to block beta$_1$ receptors rather than beta-2 receptors: include: Acebutolol (Sectral); Atenolol (Tenormin); Betaxolol (Kerlone, Betoptic); Bisoprolol (Zebeta); Esmolol (Brevibloc); Nebivolol (Bystolic); Metoprolol (Lopressor, Toprol-XL).

Beta-blockers with intrinsic sympathomimetic activity (ISA) include: Acebutolol (Sectral); Carteolol (Ocupress); Penbutolol (Levatol); Pindolol (Visken).

Beta-blockers that also block alpha-blockers include: Carvedilol (Coreg, Coreg CR); Labetalol (Trandate).

Beta-blockers that are non-selective, do not have ISA, and do not block alpha-receptors include: Levobunolol (Betagan); Metipranolol (OptiPranolol); Nadolol (Corgard); Propranol (Inderal, Inderol LA, Innopran XL); Sotalol (Betapace, Sorine); Timolol (Betimol, Biocadren, Istalol, Timoptic). Sotalol is unique because it blocks potassium channels in the heart.

Types of Angiotensin-Converting Enzyme Inhibitor Drugs

Lotensin (Benazepril); Capoten (Captopril); Vasotec (Enalapril); Monopril (Fosinopril); Prinivil, Zestoretic, Zestril (Lisinopril); Aceon (Perindopril); Accupril (quinapril) Altace (Rampril); Mavik (Trandolapril)[46] .

Objectives

Students will be able to identify the relationship of enzymes. Enzymes are very specific organic molecules that react only on one specific substrate. After observing how enzymes and substrates react they will be able to prepare a visual presentation of this reaction and explain why each enzyme is unique for a specific substance. Students will have the opportunity of testing how the enzyme substrate reaction is used in the kitchen. Students will be able to make model of a typical neuron. They will explain how structure determines function

at multiple levels of organization. Students will be able to identify specialized structures and regions of the neuron and how they function. Students will be able to see how certain drugs such as nicotine can affect an organism and make predictions on how it enters into the cell and how it affects organisms. Students will be able to explain cell functions and processes in terms of chemical reactions and energy changes. Students will be able to conduct an Internet and written material search about Beta-blockers. Students will be able to write an integrated report discussing the role of Beta-blockers and why it is a successful form of therapy for cardiovascular patients.

Strategies

I will use many different strategies in this unit. Effective teaching encompasses many different instructional strategies. In order for me to teach effectively and meet the needs of all students I have to address all of the different learning styles in my class. I will incorporate brainstorming techniques as a way of encouraging my students to focus on the topic. Students will have the opportunity to express possible answers, relevant words and ideas using this technique. I will use Problem Based Learning as a means of allowing students to consider all of the possible factors and find a solution. All ideas are accepted initially and the students will determine the best solution and not the easiest solution.

Laboratory investigations will be conducted in this unit. Laboratory experiments provide a "hands on" experience for students to visually see was is going on. Students will have the opportunity to examine how a common drug such as nicotine can affect fish. Students will also examine how nicotine affects the cell at the molecular level. The laboratory investigation allows students to visualize the role of the drug on an organism. Hands on experimentation are an important in the science classroom. It tends to crystallize concepts that may appear to be vague to a student. Laboratory investigations are fun and students retain information at a higher level when they have fun.

Research projects will be given in this unit. While doing research, students will have the opportunity to practice reading for a specific purpose, record information, sequence and organize ideas. This is a good way to increase writing and literacy skills. Students will prepare an Expanded Linear String graphic organizer when they explain how enzymes and substrates work.

A large amount of vocabulary is incorporated into this unit. A word wall will be developed and displayed when using this unit. They will support the teaching of important general principles about words found in this unit and how they work. They will provide a visual map to help children remember connections between words and characteristics that will help them form categories.

Finally the students will prepare a Powerpoint and deliver the presentation in class. The presentation is another way for students to inform their peers about what they learned about the heart medications. The presentation is a good way of providing public speaking training. Being able to verbally communicate effectively to other individuals is important in school, business and life.

Classroom Activities

Students will develop a better understanding of how drugs work when laboratory investigations, graphic organizers, video analysis, Q & A, Internet investigations and Powerpoint are incorporated.

Activity #1

Behavioral objectives for this activity include: (1) students will learn about the role enzymes play in a chemical reaction; (2) students will learn that each enzyme has a unique three-dimensional shape, including a surface grove called an active site, which fits a specific substrate.

If the shape of the enzyme active site is altered or removed, an enzyme can no longer work. Catecholase is an enzyme present in most fruits. This enzyme causes cut or bruised fruit to turn brown in the present of atmospheric oxygen. The product of this reaction is a polyphenol. Polyphenol is the brown substance that accumulates on plants when fruits or vegetables are exposed to the air. The color changes are extremely noticeable in fruits and vegetables that have white flesh. White potatoes and apples fall into this category. They tend to turn brown very quickly once the flesh is cut. The process of browning is prevented whenever these two substances are submerged in water. Divided the students into groups of two.

Materials: apples, white potatoes, plastic knife, metal butter knife, lemon wedges, paper plate, paper towel. Give each group two apples and two potatoes, one plastic knife, lemon wedge and a paper towel. Ask the students to cut the apple and the potato in half using the plastic knife, making sure that you wipe off the knife thoroughly after each use. Place one piece of apple and one piece of white potato on a paper plate. Rub one piece of apple and one piece of potato with a lemon. Place the other piece of apple and potato on another paper plate. Do not rub it with lemon. This reaction is going to take approximately 25-30 minutes.

While the reaction is taking place it a good opportunity to explain the importance of the active site and specificity in enzymes. At the end of the designated time ask students to describe what they observe. Ask the students to brainstorm and develop reasons why the pieces rubbed with lemon juice did not turn brown? The lemon juice prevents the process of browning because it has a low pH factor. The cofactor of Catecholase is a copper ion. The copper ion is easily removed by changing the pH surrounding the enzyme. The low pH of the lemon juice causes the copper cofactor to split away from Catecholase enzyme, after which the enzyme will no longer work. Water has a pH that is considered neutral. It doesn't affect the enzyme; it prevents the availability of oxygen. Oxygen is an important reactant in this reaction.

Activity #2

(Two day assignment provides the backbone for the Enzyme-Substrate Complex)

The behavioral objectives for this activity include: (1) students will conduct a web search about the enzyme-substrate complex; (2) They will prepare a model that will best illustrate how the enzyme-substrate complex works. Encourage students to use all types of materials; (3) students will prepare a written statement that will illustrate their knowledge about this type of reaction. Display the models around the classroom along with the written statement prepared statements.

Activity #3

Behavioral objectives for this activity: (1) students will learn the importance of statistical studies; (2) they will learn how to use the Internet to gather information about a specific population: (3) they will learn the benefits of conducting clinical trails. Materials: binders and portable labtop computers will be given to each student in the class.

Divide students into groups of four. Each group is responsible for gathering clinical trial statistics on the effect of beta-blockers in the following populations: African American males, females; Hispanic males, females; Caucasian males and females. Each group will select a specific city from the following choices: Philadelphia, PA; Dallas, TX; Los Angeles, CA; Miami, FL; Detroit, MI; Columbia, SC; New York City, NY; Seattle, WA.

Once each group has selected the city they will brain storm and develop strategies for collecting information. Each group is responsible for developing a Powerpoint presentation indicating the results of the Statistical Study. Presentation should include the following: 15 slides, charts/graphs, color; all members in the group must participate in the presentation, conclusion based on data presented, along with animated slides. A hard copy of the presentation should be given to teacher one day prior to presentation. The hard copy will be used to make enough copies for each student in the class. The presenters prior to the presentation will give out copies. This will allow the audience to make notes on each slide. Students can place presentations into binder given out at the beginning of the class.

Activity #4

Behavioral objectives for this activity include: (1) students will observe how a drug can effect the heart rate of an animal (2) they will learn how to examine and determine the heart rate in water fleas (3) students will learn how to prepare a hypothesis and conduct experimentation showing the effects of a stimulants and heart rates.

Materials: Water fleas, distilled water, plastic micropipettes, yeast, compound microscope, prepared coffee, stopwatch, and deep welled clean microscope slide. Preparations prior to lab: teach students how to use a stopwatch preparation of water flea habitat. Order water fleas from Carolina Supply Company and follow instructions according to supplier. Distilled water should sit 2 days prior to placing in water fleas; yeast will serve as the food for the fleas. Place the following question on the whiteboard: What do you think will happen to the heart rate of the water flea when coffee is introduced into it's environment? Students will develop several ideas about what they think will happen to the heart rate of the water flea. Introduce the caffeine molecule to the class via lecture. Show pictures of the caffeine molecule on the whiteboard. You can download an image of caffeine from several Internet sites. Prepare a deep well slide using one water flea, Place under low objective lenses. Students will observe the heart of the water flea beating. Once they have observed this students can count the number of beats for one minute using a stopwatch. Record results. Using the micropipette place one drop of coffee into the well. Students will observe and count the number of beats for one minute using the stopwatch. Students should prepare a statement discussing the conclusions reached from this experiment. Experiment and results should be written into lab book.

Activity #5

Behavioral objectives for this activity include: (1) students will learn about a neuron; (2) students will learn why neurons have such an odd shape and how it supports the job performed by the neuron; (3) students will prepare a model of a neuron; (4) students will use creativity when making models of a neuron.

When teaching about the neuron it is important to have a visual representation of a neuron on the board (smart). The following parts should be identified: Dendrite, Axon, Nodes of Ranvier, Axon Terminals, Myelin Sheath, Cell Body (Soma) and Nucleus. After identifying the parts of the neuron explain the function of the neuron. Neurons are responsible for passing signals; this is important for brain communication. Signals come to the neuron through the dendrites at the top of the neuron. Identify the three types of neurons found in the body. The three types of neurons are: sensory, motor and interneuron Sensory neurons send information toward the central nervous system, motor neurons send information away from the central nervous system, and the interneurons relay messages between sensory and motor neurons. The signal passes down the axon and travels to the next neuron. Types of neurons: bipolar neurons have two extensions from the cell body, pseudounipolar neurons have two axons and the multipolar neurons have multiple extensions but only one Neurons do not resemble any other type of cells. Students have an opportunity to be creative when they make their model of the neuron. Display the models around the classroom along with write-ups.

Activity #6 Demonstration

Behavioral objectives for this activity: (1) students will learn how nicotine affects homeostasis in goldfish; (2) students will investigate the affect of nicotine on cells.

Materials: Two round goldfish bowls, four goldfish (only one goldfish is used in the demonstration), rubber bulb, one large "T" shaped glass tubing, 5 inch of rubber tubing, one cigarette, small fish net. The extra fish will serve as backup specimens. Fill one goldfish bowl with clean water, leaving three inches from the surface to the top of the bowl. Repeat this procedure with the other fish bowl. Put the goldfish into the bowl containing the clean water. Attach the filter end of the cigarette to the rubber tubing. Attach the rubber bulb to one end of the "T" glass tube, and attach the rubber tubing with the cigarette to the other end. Light cigarette and begin to squeeze the rubber bulb. Place the long end of the glass tube into the water. Continue to squeeze the rubber bulb. Cigarette smoke is being diffused in the water. Ask students to observe the movements of the goldfish. Eventually the goldfish rolls onto the side. Scoop up the goldfish into the net and place it into the second fish bowl. Ask students to develop some predictions explaining the behavior of the goldfish when it was placed into a smoke filled environment.

Introduce students to the nicotine molecule. Illustrate the chemical formula on the smart board. Nicotine is a water-soluble molecule found in tobacco leaves. It is also used as a pesticide. Nicotine increases the heart rate, blood pressure and constricts the blood vessels. When the blood vessels constrict the blood flow decreases and the heart has to work harder. Beta-blockers are used in patients who suffer from this condition. The lifestyle of the patient has to change and he/she has to stop smoking. Beta-blockers prevent the transmission of certain neuroreceptors found at the end of the cell. When the Beta-adrenergic receptors are blocked the heart rate decreases and the blood pressure drops.

Ask students to come up with a conclusion that will justify why the goldfish flipped over on its side in the smoke filled water. Show the relationship between the job done by the heart and how it caused a decrease in oxygen coming from the gills.

Activity #7

Behavioral objective for this activity: (1) students will stimulate the effect of constricted blood vessels caused by nicotine. (2) students will learn why water-soluble molecules enter into the cell at a faster rate by examining the role of the cell membrane.

Materials: ten Styrofoam cups, five straws (soda), five coffee stirrers, ½ of Deer Park Spring Water. Get ten student volunteers of five females and five males. Student volunteers should be of various sizes. Give the 10 straws to the student volunteers making sure that the types of straws are dispersed evenly. On the count of three ask the students to sip as much water as possible. Request the other children to cheer the volunteers by saying "Go, Go". Observe the reactions of the students and the amount of water consumed. Students drinking water out of the smaller straw have a harder time of getting water. The volume of water passing through the coffee stirrer was smaller when compared to the volume of water passing through the soda straw. It will take twice as long to drink the water in the cup. Students using the smaller straws had to suck harder on the straw. This experiment illustrates how the heart works harder whenever nicotine is in the system.

Student Resources

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http://go.hrw.com This website is the home page for the publisher of our textbook: it has activities and worksheets directly related to the material in the text.

Johnson, George B., PhD. And Raven, Peter H., Holt Biology, Austin: Holt, Rinehart, and Winston, 2004. This book is recommended for the biology course, as approved by the School District of Philadelphia.

www.SciLinks This is an online website developed by the National Science Teachers Association. It contains content specific activities and provides links to other information you can use for projects, reports, and research papers.

Appendix-Content Standards

The Pennsylvania Academic Standards for Biological Sciences, which will be addressed in this curriculum, was taken directly from the Core Curriculum Standards Alignment and Educational Resource Guide for the School District of Philadelphia. They include the following:

3.3 Biological Sciences Standards (A, B)

A. Explain the structural and functional similarities found among living things.

1. Explain the relationship between structure and function at the molecular, cellular, tissue and organ level.

B. Describe and explain the chemical and structural basis of living organisms.

1. Explain how cells store and se information to guide their functions.

2. Explain cell functions and process in terms of chemical reactions and energy changes.

Endnotes

1. "Be One in a Million this American Heart Month," The Center for Disease Control and Prevention, last modified February 3, 2012. www.cdc.gov/dhdsp/american_heart_month.htm.
2. ibid, 1.
3. "Cardiovascular Drug Delivery-technologies, markets and companies," http://www.prnewswire.com/news-releases/cardiovascular-drug-delivery—technologiesmarkets-and companies-138466949.html.
4. ibid, 1.
5. "Cardiac Medications," http://www.heart.org/idc/groups/heart-public/wcm/hcm/documents/downloadable/ucm_304568.pdf.
6. ibid, 2.
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8. ibid, 3.
9. ibid, 4.
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11. J.M. Cruickshank and B.N.C. Prichard, "Beta Blockers in Clinical Practice." 1.
12. "Ergot," http://encyclopedia2.thefreedictionary.com/Ergot
13. J. M. Cruickshank and B.N.C. Prichard, "Beta Blockers in Clinical Practice," 1.
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15. ibid, 2.
16. ibid, 1.
17. ibid, 1.
18. ibid, 1.
19. ibid, 1.
20. Kostis, Defelice, "Beta Blockers in the treatment of Cardiovascular Disease." 1.
21. ibid, 3.
22. Baughman, Baumgartner, "Treatment of Heart Disease." 191.
23. ibid, 192.
24. ibid, 6,7.
25. ibid, 9.
26. ibid, 9.
27. ibid, 9.
28. ibid, 9.
29. http://faculty.washington.edu/chudler/auto.html
30. ibid.
31. Epstein, Brunner, "Angiotensin II Receptor Antagonists," 329.
32. ibid, 330.
33. ibid, 330.
34. ibid, 330.
35. Opie, "Angiotensin Converting Enzyme Inhibitors," 61.
36. "Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatine and/or serum potassium concentration rises," http://ndt.oxfordjournals.org/ at Yale University, 1974.
37. ibid, 1974.
38. ibid, 1974.
39. ibid, 1974.

40. ibid, 1974.
41. Opie, "Angiotensin Converting Enzymes Inhibitors,"48.
42. ibid, 48.
43. Ibid, 48.
44. ibid, 50.
45. Schachter, "ACE Inhibitors: Current Use and Future Prospects," 46.
46. "List of Beta Blockers," http://senior-heatlh.emedtv.com/beta-blockers/list-of-beta-blockers/list-of-beta-blockers/html.

Annotated Bibliography

"*Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatinine and/or serum potassium concentration rises*,""http://ndt.oxfordjournals/at Yale University. I974 (assessed July 17, 2012)

"Be one in a Million this American Hear Month, "Center for Disease Control. January 30, 2012. http://www.cdc.gov/dhdsp/american_month.htm (assessed July 9, 2012) Website provides information about the latest initiative taken by the federal govern Government.

Baughman, Kenneth L., Baumgartner, William A. "*Treatment of Advanced Heart Disease*. New York: Taylor & Francis Group, 2006. 191-192.

"Cardiac Medications, "American Heart Association. http://www.heart.org/ide/ groups/heart-publicwcm/Ahem/documents/downloadable/ucm_304568.pdf. 2,3,4. (assessed July 11, 2012).

Website classifies the ten groups of medications used to treat cardiovascular diseases. It provides a very used chart because it will allow you to see what the the medication does in the body and the reason for taking a specific type of heart medication.

"*Cardiovascular Drug Delivery-technologies, markets, and companies.*" February 1, 2012. http://www.prnewswire.com/news-releases/cardiovascular-drug-delivery—technologiesmarkets-and-companies-138466949.html. (assessed July 9, 2012).

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Epstein, Murray, MD, FACP, Brunner, Hans R. MD, "*Angiotensin II Receptor Antagonists.*" Philadelphia: Hanley & Belfus, 2001. 329,330. Book provided a comprehensive look at the role played by Angiotensin II receptor Antagonists.

Kostis, John B. MD, DeFelice, Eugene A. MD, "*Beta Blockers in the Treatment of Cardiovascular Disease*," New York: Raven Press, 1984. 1,3. Book provides description of the information about how Beta-blockers are used in Treating cardiovascular disease.

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Opie, Lionel H. MD. PhD, FRCP "*Angiotensin Converting Enzyme Inhibitors*," New York: Authors' Publishing House, 48, 61. Book describes the clinical basis of using ACE inhibitors.

Schachter, Michael, MRCP, "ACE Inhibitors, Current Use an Future Prospects," United Kingdom: Martin Dunitz LTD, 68. Book provides

background information how ACE inhibitors is used to treat various Form of cardiovascular disease.