Lab 1: Resources

Introduction:

Diabetes Mellitus, which is also known as sugar diabetes, is a disease where the body either has a problem with producing insulin or properly utilizing insulin (1). Insulin is a naturally occurring hormone in the body which facilitates the transport of glucose into cells (7). Recent statistics from the American Diabetes Association have shown that approximately 20.8 million people in our country are diabetic which means that seven percent of the population has a form of the disease (1). Type 1 diabetes, also known as juvenile diabetes, is usually discovered at a young age. Here the body does not produce any insulin, which leaves the body no way to monitor glucose transportation (1). This lack of insulin causes severe problems and is why this form of diabetes is usually noticed early on. Type 2 diabetes, which is the most common, can result from two ways. First, the body may not be producing sufficient amounts of insulin or secondly the cells become insulin resistant (1). When this occurs, insulin is still being produced but the cells do not respond to its commands (1). Type 2 diabetes has been associated in our country with excessive weight gain and the rise of obesity (1). This paper will not only address the two different types of diabetes but will also describe physiological concepts having to do with diabetes. These concepts include the membrane transportation of glucose and the secretion of insulin, how the body regulates hypoglycemia, how ketoacidosis occurs, and how obesity can lead to type 2 diabetes.

Concept 1: Membrane Transportation of Glucose and the Secretion of Insulin

The human body is comprised of cells. These cells have a variety of shapes and functions but they all have common features. One common feature among all cells is a plasma membrane which acts as a specialized barrier between the inside and the outside of the cell (3). Plasma membranes are composed of two layers of phospholipids and also proteins, cholesterol, and carbohydrates (3). These membranes form so that the outer layer is polar and the inner layer is non polar (3). Molecules of all shapes and sizes are in constant need to enter and leave the cell but unless these molecules are tiny enough to slip through the plasma membrane, they can’t get through unless they receive help (3). Glucose is one of these larger molecules which receive help from transmembrane proteins (7). There are two ways for glucose to get across the plasma membrane. The first is a form of passive transport called facilitated diffusion (3). Passive transport requires no energy to be spent in order to move glucose across the plasma membrane; instead it relies on the concentration gradient of glucose (3). Concentration gradient refers to the difference in concentration of a substance between regions, in this case between the outside and the inside of a cell (7). If the concentration of glucose is higher outside of the cell, glucose can enter the binding site of a carrier protein which are usually specific for certain substances (3). The carrier protein then performs a conformational change (a change in shape) to move the substance from high to low concentration (7). The second form of glucose transport is unlike passive transport because it requires energy to be spent to move glucose against its concentration gradient (3). Secondary active transport, specifically cotransport, once again utilizes a protein to move glucose but it also needs a moderator molecule as well (3). The carrier protein binds to the moderator molecule on its high concentration side and binds to glucose on its low concentration side (3). The carrier protein then changes its shape and moves the moderator down its concentration gradient while at the same time moving glucose up its concentration gradient (3). Both molecules are then released on their respective sides.

But none of these glucose transportation processes will occur unless insulin tells cells to insert glucose transport proteins called GLUT 4 into their membranes (4). Insulin is released by the beta cells located in the islets of Langerhans in the pancreas when glucose levels in the blood begin to rise (4). Insulin is then delivered to adipose tissue cells, skeletal muscle cells and the liver where it binds to insulin receptors (4). The receptors inform the cells to insert GLUT 4 proteins into their plasma membrane which allows glucose to enter the cell (4). As glucose enters the cell it causes the blood glucose levels to decrease and negative feedback to occur. Here the pancreas stops releasing insulin so some glucose is left in the bloodstream and not taken into cells (7).

Concept 2: Contrasting the 2 types of Diabetes

Type 1 diabetes makes up 5-10% of all cases and usually occurs in pre-adolescence (8). This form of diabetes is sometimes referred to as an autoimmune disease because it results from the destruction of beta cells by the immune system (4). If the immune system begins to kill beta cells then the pancreas can’t produce insulin. If insulin is not produced then cells are not told to insert GLUT 4 proteins into their plasma membrane. By not having GLUT 4 proteins in their membranes, glucose can not enter the cells and as a result blood glucose levels remain high (4). This high level of glucose is called hyperglycemia (7). During hyperglycemia the pancreas also secretes more glucagon because its alpha cells are insulin dependent (7). Since insulin isn’t available to tell these cells to take in glucose, the cells are lead to believe that glucose levels are lower than they actually are, thus they secrete glucagons to make up for the missing glucose (7). Hyperlipidemia which is an excess of fatty acids and other lipids in the blood can also occur in type 1 diabetes (7). Hyperlipidemia is a result of the excessive breakdown of lipids coupled with the suppression of forming triglyercides (7). Also, since glucose is not being able to be broken down by cells for energy, the body has to resort to breaking down fatty acids (7).

Type 2 diabetes accounts for 90% of people with diabetes and has been shown to appear after the age of 30 (8). This type of diabetes occurs when the synthesis and secretion of insulin by beta cells decreases or target cells become resistant to insulin (8). In normal people without diabetes, beta cells can adapt to insulin resistance by simply increasing their insulin secretion (5). However, in diabetic patients, this normal compensatory mechanism fails over time and impaired glucose tolerance develops (5). After this mechanism fails, insulin secretion after a meal is delayed and hyperglycemia occurs as it did in type 1 diabetes (5). As the functioning of the beta cells continues to decrease so too does their anatomy. A morphologic change such as a reduction in the beta cell mass of the pancreas occurs and as a result there is an increase in the ratio of alpha cells to beta cells (5). Since alpha cells secrete glucagon there also becomes an increase in the ratio of glucagon production to insulin production (5). This causes problems with glycemic control over time and results in the development of type 2 diabetes (5).

Concept 3: How Ketoacidosis Develops from Diabetes:

As discussed above, breaking down too many fatty acids instead of glucose molecules for energy can result in ketoacidosis (7). Ketoacidosis is mainly found in type 1 diabetes as a result of incorrect insulin adjustment (9). When the body has no glucose to use for energy it has to resort to breaking down fats to obtain energy (7). After the body breaks down fat, it is left with glucose and large amounts of free fatty acids (10). These free fatty acids then go through a process called oxidation, in which they lose an electron (10). After the free fatty acids are oxidized, large amounts of acetyl-CoA molecules are then derived and are sent to the liver mitochondria (9). Acetyl-CoA molecules are sent to the liver mitochondria instead of fed into the Krebs cycle because the large amounts exceed the capacity for its conversion to carbon dioxide (9). The liver mitochondria then perform a process that condenses the molecules into acetoacetyl CoA (9). The mitochondria then form β-hydroxy-β-methylglutaryl CoA (HMG-CoA) which is catalyzed by HMG-CoA synthase (9). With the help of the enzyme HMG-CoA lyase, the mitochondria then cleave (split) the HMG-CoA into acetoacetate (9). Acetoacetate can either remain acetoacetate or it can be converted to β-hydroxybutyrate (9). Either way, both acetoacetate and β-hydroxybutyrate are known as ketone bodies and are the most common molecules found in diabetic ketoacidosis (9).

With an excess of ketone bodies floating around in the bloodstream, there is an increase in the hydrogen ion concentration (9). This increase in hydrogen ions causes the pH level in the blood to drop to an acidic level because there is an increase in the ratio of H^+ cations compared to OH^- anions (10). This drop in pH is very dangerous to the body because once the pH drops below a certain level, enzymatic reactions have a difficult time taking place (3). In acidic conditions some enzymes become denatured, that is they lose their correct shape and thus become useless in catalyzing a reaction (3). Also in ketoacidosis, the central nervous system becomes depressed (7). This can lead to a coma or even worse death (7). Ketoacidosis is treated with insulin injections (9). By injecting insulin, the body can then use glucose as its main energy source instead of breaking down fats for energy (9). If fats are not broken down then ketone bodies will not be produced and the blood pH levels will start to return to normal.

Concept 4: How hypoglycemia is regulated in the body

In both types of diabetes, hypoglycemia is a common problem. In normal people without diabetes, glucose levels are regulated through a homeostatic process called negative feedback (7). Usually levels are kept tightly around the set point of 90 mg/dL (2). Hypoglycemia refers to the situation when glucose levels drop far below the set point to around 75 mg/dL (2). This is causes severe problems because the brain cannot synthesize its own glucose and it can only store small quantities, thus it constantly requires glucose from the blood (2). As glucose levels fall to about 80 mg/dL, beta cells sense the drop and inhibit insulin secretion (2). This is the first line of defense and it allows glucose to remain in the blood stream (2). But if glucose levels continue to drop to 70 mg/dL, glucagon starts being secreted by the alpha cells (2). When glucagon is secreted it stimulates glucose production in the liver by two processes, glycogenolysis and gluconeogenesis (2).

Glycogenolysis is the process of breaking down glycogen into individual glucose molecules (7). First the liver breaks down glycogen into glucose-6-P, then an enzyme found in the liver, glucose-6-phosphatase, catalyzes the further breakdown of glucose-6-P into glucose which can be sent into the blood stream to be used by cells (7). Gluconeogenesis refers to the process of making new glucose molecules and it can be done by using glycerol, lactate, and amino acids (7). If glycerol or lactate is used, they are first formed into glycerol phosphate and pyruvate respectively (3). These end products are then fed into glycolysis backwards which combines two pyruvates to form one glucose molecule (7). If amino acids are used they are also converted to pyruvate and then proceed through glycolysis backwards (7). If neither of these processes works the body has one last line of defense: secretion of epinephrine by the adrenal glands (2). Epinephrine inhibits the release of insulin which stops glucose from being removed from the blood and helps glucagon secretion (2). The release of epinephrine keeps glucose in the bloodstream so that the concentration remains around its set point.

Concept 5: Physiological Connection Between Type 2 Diabetes and Obesity:

Type 2 diabetes has been found more often in obese individuals than lean individuals and with the rise of obesity worldwide, the link between obesity and diabetes has been a focus of many studies (1). Firstly, there have been endocrine mechanisms associated with fatty acids which cause diabetes because as obesity increases so too does the concentration of fatty acids in the body (6). Fatty acids are used by the body for energy as energy levels begin to decrease in the body (6). By having excess fatty acids floating around in the blood stream it has been found that there has been competition between the fatty acids and glucose in insulin-responsive cells (6). Also, as fatty acid concentrations rise, they trigger insulin resistance by activating serine and threonine kinases (6). These kinases are responsible for inhibiting insulin signaling in the body (6). Secondly, inflammatory mechanisms in obese individuals play an important role in the development of diabetes (6). Inflammatory stimuli affect kinases in the body, especially

JUN N-terminal kinase 1 (JNK1) (6). In obese individuals JNK1 activity is increased in liver, muscle, and adipose tissue (6). This is a major problem because decreasing levels of JNK1 is what prevents insulin resistance (6). Thus, by increasing the level of JNK1, insulin resistance is not prevented and type 2 diabetes can occur. Finally, neural mechanisms which are affected by obesity produce changes that cause diabetes (6). In normal weight individuals, the brain sends signals which regulate homeostasis between feeding behaviors and metabolism, but in obese individuals this feedback system is not regulated properly (6). When this feedback system is not regulated properly, feeding occurs even when the body is not hungry. This causes an increase in fatty acids which results in insulin resistance (6).

Conclusion:

Diabetes is a life changing disease that is unfortunately becoming increasingly common in our country. With the growing numbers of diabetic patients each year, it is a focus of many to educate our society on this disease. By teaching people how they can prevent the onset of diabetes by changing their lifestyle and decreasing the number of obese individuals, thousands of new cases could be prevented. But if people decide not to prevent the disease, they should be educated on how to manage the disease. They should learn about the physiological effects of diabetes, such as hypoglycemia and ketoacidosis, so that they can avoid these dangerous side effects. Although there is no cure for either type of diabetes, researchers and scientists are discovering more and more physiological aspects of the disease and with their continued devotion coupled with the rise in its prevalence, I believe diabetes will soon be an even more manageable disease.

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