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Combating diabetes: A study on the fundamental mechanism behind the effect of sugar on cellular respiration carried out by *Saccharomyces Cerevisiae* and catabolic pathways related to hyperglycemia

Abstract. Prompted by the seriousness and urgency of diabetic illnesses in the modern era, a major cause of various health conditions, this study was designed to explore and investigate the potential implications for diabetes research using the relationship between yeast respiration and glucose homeostasis. Saccharomyces Cerevisiae rapidly utilizes sugars in the process of cellular respiration both aerobic and anaerobic. While it is widely recognized that yeast's capacity to ferment using glucose results in the production of energy, the study starts by examining the effect of six different sugars of the same molar mass - glucose, sucrose, fructose, galactose, lactose, and maltose - on the rate and amount of carbon dioxide produced in Saccharomyces Cerevisiae in a yeast medium. The yeast-sugar mixture is connected to a hose that leads to a water displacement system for measuring the volume of carbon dioxide produced. As the yeast uses the sugars to respirate and undergo glycolysis, carbon dioxide is collected in a container of water, and the amount of increasing carbon dioxide is determined by measuring the decreased volume of water. It could be found that glucose, fructose, and sucrose enabled fermentation while sucrose yielded carbon dioxide at a delayed rate. Exploring the fundamental mechanism behind yeast respiration, the information obtained can be used to understand the process of glucose homeostasis and catabolite repression in yeast fermentation. Correlating the insulin transduction pathway and Snf1 protein kinase to the process of glycolysis, we hope to facilitate diabetes research. Using yeast as the experiment's model system, the catabolic mechanism and respiration process of a eukaryotic model will suffice our understanding of hyperglycemia in type 2 diabetes. The uptake of glucose and other sugars, along with how insulin sensitivity is induced through the coordination of carbon metabolism pathways will be relevant in researching potential treatment methods for diabetes.

Keywords. Diabetes, cellular respiration, fermentation, glycolysis, insulin, hyperglycemia, insulin transduction pathway, glucose homeostasis, Snf1 protein kinase, catabolite repression

1. Introduction

1.1 Purpose of the Study

Nowadays, diabetes is a long-term impairment in the body that affects more than 10 percent of the global adult population. Although depending on the individual, the dichotomy of diabetes is that the disease can be life-threatening if left disregarded and untreated, but the patient can learn to manage it by taking the appropriate treatments and keeping a healthy lifestyle. Adhering to the appropriate treatment methods for the disease can positively impact one's quality of life.

The causes and treatments for diabetes vary among the many types of diabetes such as prediabetes, type 1 diabetes, type 2 diabetes, and gestational diabetes. According to the WHO (World Health Organization), more than 95% of people with diabetes suffer from type 2 diabetes, formerly called non-insulin-dependent diabetes or adult-onset diabetes. The effect of hyperglycemia - high blood glucose levels - can develop a wide range of complications, from temporary symptoms to damaging conditions. Generally, pharmaceutical methods of injecting insulin for diabetes type 1 and individual efforts to treat diabetes type 2 have been accepted as ways of reducing or avoiding serious complications of the disease. However, aside from the conventional method of treating diabetes, which includes but is not limited to using insulin pumps and/or injections, prescription of medication, diet, and exercise, the study hopes to tackle the disease by investigating the mechanism behind glucose homeostasis of *Saccharomyces cerevisiae* on a cellular level.

The following study attempts to demonstrate the effectiveness of *S. cerevisiae* in the potential treatment of type 2 diabetes. The study focuses on the catabolic pathways in which enzymes and insulin signals can be coordinated to stimulate insulin sensitivity. Researching catabolic repression of glucose during yeast fermentation can help understand the mechanism behind sensing and signaling extracellular glucose levels, giving insight into how to manage hyperglycemia through the coordination of various cellular pathways.

1.2 Background

1.2.1 Diabetes

Diabetes is a chronic disease in which blood glucose, or blood sugar, is higher than its normal range in the human body. The accumulation of glucose in the bloodstream is the product of the food intake and becomes the main source of energy for human activity and body temperature maintenance. A hormone that facilitates this process of glucose getting into one's cells and being used for energy is insulin. Insulin is produced by the pancreas and it is critical to managing glucose homeostasis in one's bloodstream. If insulin fails to proceed in aiding glucose to be used for energy, glucose would stay in one's blood and be unable to reach the cells. An overflow of glucose in the bloodstream would cause hyperglycemia, the effect of diabetes, and various health issues. The irony of diabetes is that the disease has no cure, but one may manage and take care of diabetes daily.

Diabetes is commonly subdivided into two types - type 1 and type 2 diabetes. Type 1 diabetes refers to when one's body fails to make insulin from the destruction of cells in the pancreas which are responsible for making insulin. It is a disease of the immune system, while genetic factors or viruses may also trigger the destruction of cells producing insulin. Patients diagnosed with type 1 diabetes need to take insulin every day to control blood glucose levels and prevent hyperglycemia. Meanwhile, type 2 diabetes occurs when one's body does not utilize insulin at a proper level, thus the body being insulin resistant. Type 2 diabetes makes up for most cases of the disease, usually developing after adulthood. In addition to factors related to age, ethnicity, and genetic inheritance, having high blood

pressure, along with being overweight or lacking physical activity are the main risk factors for developing diabetes type 2. The study refers to type 2 diabetes when talking about the disease.

Patients diagnosed with diabetes suffer from disorders of the circulatory, nervous and immune systems. Symptoms of type 2 diabetes can range from risk factors as common as high blood pressure to heart disease and polycystic ovary syndrome (PCOS). Daily symptoms which are easy to neglect to include increased thirst, frequent urination, increased hunger, blurred vision, areas of darkened skin, etc. Because the symptoms of type 2 diabetes happen to develop at a slow rate, some patients live with it without even knowing it. However, accumulating high levels of blood glucose over a prolonged period can result in serious complications in numerous parts of the body vital for survival.

As much as diabetes is a chronic disease, its treatment methods consist of management methods that keep one's blood glucose level within the normal range. Although this helps delay or prevent the symptoms of the disease, there is no direct method of treatment that eliminates the complications at once. Centering around a healthy diet can help manage nutrition intake and keep blood sugar levels more stable. Regular physical activity along with medications depending on the specific condition of the individual will aid in maintaining the target blood glucose levels. Depending on one's complications, insulin therapy is prescribed - insulin is injected in appropriate doses and schedules, aimed to prevent continuous diabetes complications.

1.2.2 Saccharomyces Cerevisiae

<Figure 1> Saccharomyces cerevisiae,
electron micrograph

Saccharomyces cerevisiae, also known as Brewer's yeast or Baker's yeast, is used as the main subject of this study, acknowledging its unicellular nature and capacity to perform biological functions apt for eukaryotic research. Available for various biotechnological and medical applications, the organism is easily applicable to genetic manipulation due to its biological characteristics. For instance, *S. cerevisiae*'s resilience to various conditions of pH and osmolarity makes it the perfect choice for tracking its ability to fermentate. The organism is not only useful in familiar food industries such as bakery and wine production, which make use of yeast's capacity to rapidly ferment, but the biopharmaceutical field. Approximately one-fifth of biopharmaceuticals are produced by S. cerevisiae - among these are insulin, vaccines for hepatitis and human papillomavirus, and probiotic treatment for diarrhea.

Selecting *S. cerevisiae* as the subject of the study allowed the understanding of a fundamental eukaryotic system. Having a nucleus with DNA in chromosomes, its metabolic pathways can readily be experimented on to study human cellular metabolism. In the study, its capacity to perform anaerobic respiration under controlled conditions was experimented on. The various aspects of the microorganism contain the potential of providing a data basis for human cell engineering.

1.2.3 Fermentation

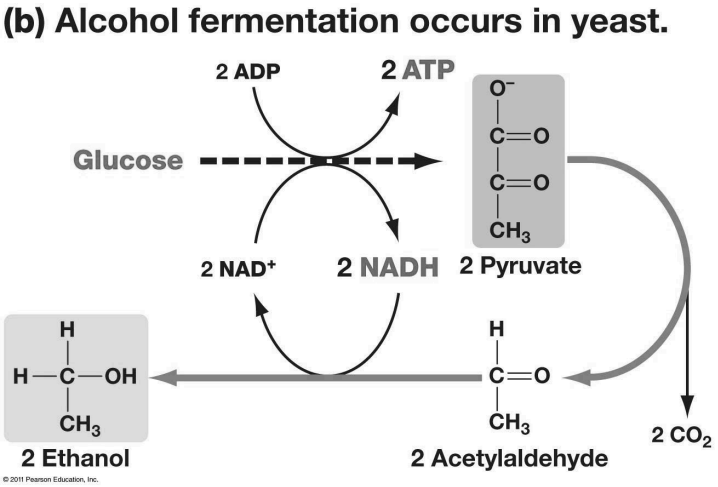
1.2.3.1 Cellular respiration

Cellular respiration is the process of breaking down glucose to produce adenosine triphosphate (ATP), an energy-carrying molecule. The main steps of cellular respiration are glycolysis, pyruvate oxidation, the citric acid cycle, and oxidative phosphorylation. The last step - oxidative phosphorylation - is a process including the electron transport chain. After the electrons are transferred from one molecule to another, releasing energy, oxygen is the molecule that accepts the electrons and allows the continuation of ATP production. Therefore, under circumstances where there is no oxygen, this process is not possible. In this case, yeasts undergo fermentation - an anaerobic process of breaking down glucose for energy. During fermentation, the yeast cells produce ATP during glycolysis, a process in which oxygen is not a contributing factor, and repeat the process through NAD+ regeneration. Classified according to the resulting product, alcohol (ethanol) fermentation, lactic acid fermentation, and butyric acid fermentation are several examples of fermentation. In this study, alcohol fermentation takes place, producing ethanol and carbon dioxide as the byproduct.

1.2.2.2 Glycolysis

Among the steps of cellular respiration, glycolysis is the initial stage that produces two net molecules of ATP. In simple terms, two phosphate molecules derived from two ATP molecules are used to modify a glucose molecule into the fructose-1,6-bisphosphate molecule; this unstable molecule is then split to form two three-carbon sugars. Each three-carbon sugar is converted to two pyruvates, each producing two ATP molecules and one NADH molecule. Therefore, two ATP molecules and two NADH molecules are produced.

In alcoholic fermentation, the electrons of NADH are used to produce ethanol from pyruvates. In detail, a carboxyl group is disconnected from the pyruvate and becomes carbon dioxide, while the pyruvates become two acetaldehyde molecules. The electrons from two NADH molecules turn acetaldehyde into ethanol, and the NAD+ produced can be used for further fermentation.



<Figure 2> Overview of the reactions that occur during alcoholic fermentation. Two NADH+ molecules produced are converted to NADH molecules, while two net ATP molecules are produced.

2. Experimental Design and Hypothesis

2.1 Method

2.1.1 Sugar

Sugar is one of the reactants of cellular respiration that are broken down for energy that powers the body. It is a type of carbohydrate - a molecule formed from carbon, hydrogen, and oxygen. Carbohydrates can be classified into monosaccharides, disaccharides, and polysaccharides - one simple sugar, two simple sugars, and a polymer of sugars respectively. The monosaccharides are the basic compounds of sugar. Glucose, fructose, and galactose are isomers - compounds that are formed from the same number and type of atoms but differ in the arrangement of atoms. Due to the identical molecular formula, $C_6H_{12}O_6$, the monosaccharides share a common molar mass of approximately 180.16g/mol. Disaccharides are formed by two monosaccharide units combined by a dehydration synthesis reaction. During the process, a water(H_2O) molecule is released, in turn resulting in a glycosidic bond in the disaccharide. Sucrose, lactose, and maltose are respectively formed from glucose and fructose, glucose and galactose, and two glucose units. Their molar mass is 342.3g/mol - twice the molar mass of two monosaccharides reduced by the molar mass of water(18g/mol).

S. Cerevisae's cellular respiration process was tested using different types of sugars. In total, six types of sugars were used: three monosaccharides - glucose, fructose, and galactose and three disaccharides - sucrose, lactose, and maltose. Though cellular respiration is widely known as a process of breaking down glucose, this study also experiments on sugars that are usually not considered direct reactants. Therefore, the following hypothesis is possible: among the certain types of sugar that enable fermentation, the rate of fermentation will vary due to the different enzyme catalysis and metabolic pathways yeast cells undergo.

Independent Variable	Type of sugar
Dependent Variable	Amount of carbon dioxide produced
Control Variable	Amount of water, temperature of water, amount of yeast, type of yeast, amount of sugar(mol)

2.2 Measures and Procedures

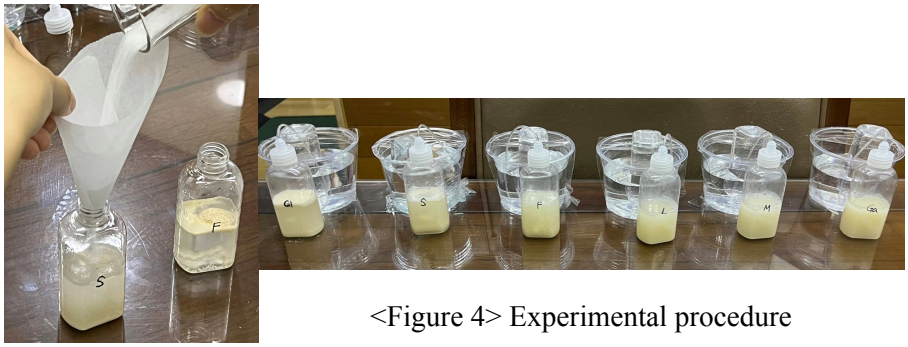
The materials used for fermentation are active dry yeast obtained from strains of S. cerevisiae, water, sugars, and water displacement systems, each used for one type of sugar. To create the appropriate environment for C. Serevisae to ferment, the water was managed to 35°C. In a container, the same amount of water and yeast was added. The sugars, however, were measured according to their molar mass. While the molar mass of monosaccharides is 180g/mol, the molar mass of disaccharides is 342g/mol due to the process disaccharides are formed: a dehydration synthesis reaction, in which two monosaccharides are combined and one molecule of hydrogen is removed. In order to use an equivalent number of sugar molecules, 2g of monosaccharides and 3.8g of disaccharides were measured. (180: 342 = 2: 3.8) For each sugar and yeast compound, 40g of water and 1g of yeast were used.

To find out which types of sugar enable respiration and to measure the rate of respiration, this study used the water displacement method. Through the displacement method, the increasing volume of

carbon dioxide is measured by a decrease in the volume of water. Carbon dioxide is a gas whose solubility in water differs according to pressure and temperature. With a water temperature of 40°C and an atmospheric pressure of approximately 101 kPa, the solubility of carbon dioxide is 1.0g/kg of water. Thus, the amount of carbon dioxide dissolved in water was considered a negligible factor in measuring the produced carbon dioxide in this study.

<Figure 3> Experimental design using water displacement method

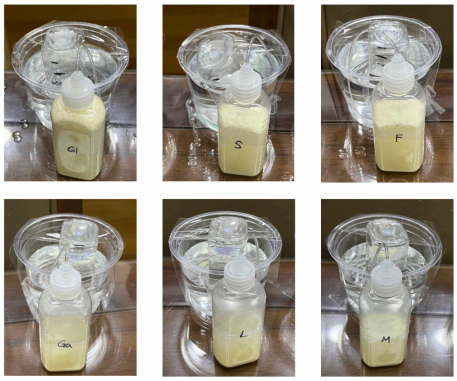
In six identical containers, active dry yeast and sugars are added. The containers are each connected to a thin hose that leads to another container filled with water of 40°C. These containers are fixed upside-down, submerged in water so that the water stays inside the containers due to atmospheric pressure. As the yeast uses sugar for respiration, the produced carbon dioxide is transferred from the container with the yeast and sugar to the container filled with water, through a hose. As the hose continues to transfer carbon dioxide, bubbles are accumulated at the top of the container, while the displaced water is pushed out from the container. The volume of gas produced was measured every ten minutes for an hour.



<Figure 4> Experimental procedure

3. Results

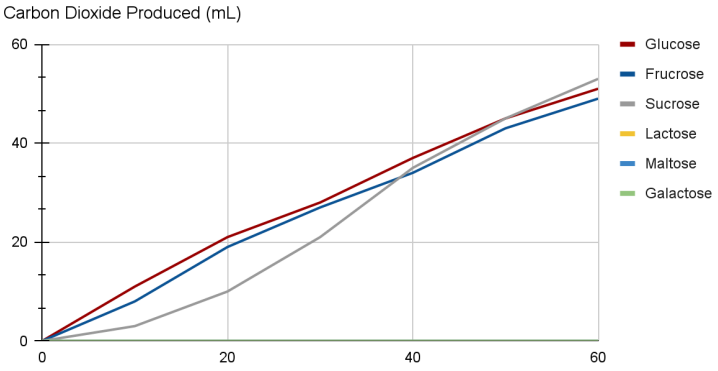
Initially, the yeast conducted aerobic respiration, using sugar and the oxygen inside the container to produce water and carbon dioxide. After all of the oxygen was depleted for respiration, anaerobic respiration took place, producing carbon dioxide and ethanol as the byproduct. After one hour of observation, whether the yeast fermented using each type of sugar could readily be determined by the volume of carbon dioxide produced. Glucose, fructose, and sucrose yielded carbon dioxide, while lactose, maltose, and galactose did not. This can be interpreted as yeast having the specific enzymes that catalyze the fermenting process using glucose, fructose, and sucrose.



<Figure 5> Results of experiment

<Figure 6> Chart(top) and graph(bottom) of results

		Type of sugar					
		Glucose	Frucrose	Sucrose	Lactose	Maltose	Galactose
Time	0	0	0	0	0	0	0
	10	11	8	3	0	0	0
	20	21	19	10	0	0	0
	30	28	27	21	0	0	0
	40	37	34	35	0	0	0
	50	45	43	45	0	0	0
	60	51	49	53	0	0	0



The x-axis indicates the number of minutes since the start of the experiment, while the y-axis indicates the amount of carbon dioxide produced(mL)

Among the sugars that enabled fermentation, glucose yielded carbon dioxide at the fastest rate. The steadily increasing amount of carbon dioxide can also be observed in the fermentation using fructose. The notable observation that can be made from the graph is the slope of carbon dioxide produced using sucrose. For the initial 40 minutes, it produced relatively less carbon dioxide than did glucose or fructose. However, the increasing slope of the graph, and the similarity between the amount of carbon dioxide produced in the final stage of the three sugars, indicate that sucrose goes through rapid fermentation after a certain period of delay. This delayed period suggests that sucrose undergoes a period of catalyzation, in which the enzymes that expedite the fermenting process make sucrose easier to use as a reactant. A difference that can explain the difference between glucose/fructose and sucrose is that glucose and fructose are monosaccharides, while sucrose is a disaccharide. Monosaccharides can directly be used for fermentation, while disaccharides have to be broken down into monosaccharides beforehand. Accordingly, sucrose necessitates a process of being broken down to glucose and fructose before fermentation. Once the sugars are broken down by enzymes, the monosaccharides can actively be used for producing energy. On the other hand, yeast does not contain the specific enzymes needed to break down lactose and maltose, nor the enzyme that enables fermentation for galactose.

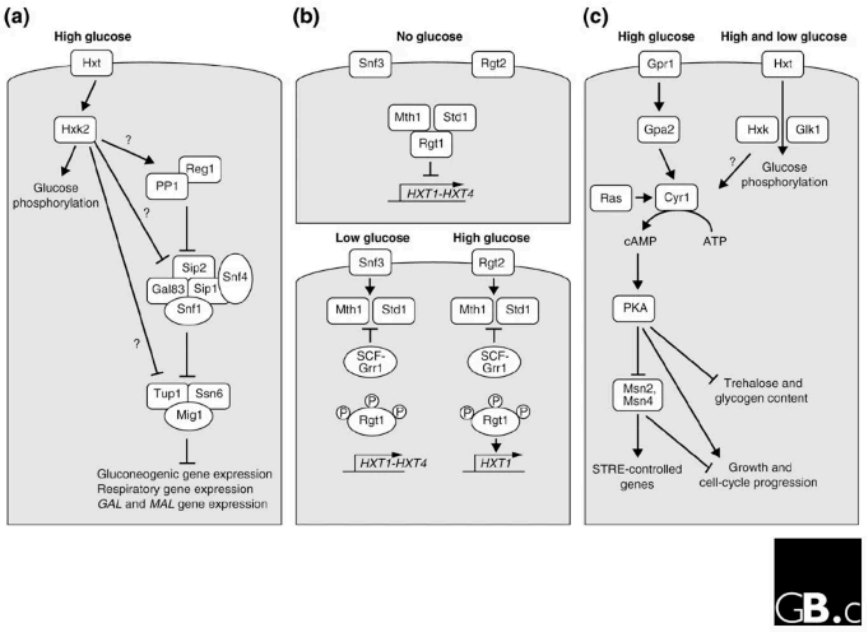
4. Discussion/Conclusion

4.1 Catabolite repression

The experiment concludes that yeast is capable of using glucose as the direct reactant for fermentation. The metabolic mechanism behind yeast's dominant utilization of glucose amid other carbon sources can be explained through yeast's glucose sensing and signaling pathways, one of which is yeast's glucose-repression pathway. Although yeasts can use various carbon sources for producing energy, it prefers to use certain carbon sources before others. This phenomenon had been called 'glucose repression', though currently 'catabolite repression' is the preferred term to indicate the dominant utilization of particular carbon sources - including glucose - over others. Yeast's genes are encoded with enzymes, which are transcripted to utilize various carbon sources for respiration. The presence of glucose, and sometimes related sugars such as fructose, repress this transcription, which results in the carbon metabolism of yeast primarily facilitating glucose use.

4.2 Glucose sensing and signaling pathways

The mechanism behind catabolite repression is correlated to the glucose-sensing pathways of yeast. The current understanding of glucose-responsive pathways in yeast are generally three pathways: the main glucose repression pathway, the Snf3/Rgt2 glucose-sensing pathway, and the Gpa1/Gpr2 glucose-sensing pathway (Ras-cAMP pathway). The first pathway triggers glucose repression when there are other carbon sources and controls yeast's carbon metabolism. The regulation of catabolite-repression activators and repressors is carried out by Snf1 signaling - the Snf1 enzyme is capable of both activating and suppressing glucose repression. This protein kinase was identified when sucrose was used for fermentation in a state of glucose limitation. It is a vital enzyme for managing cellular energy levels by regulating the level of glucose entering the cell. The second pathway regulates yeast's capacity to uptake glucose by the induction of HXT (hexose transporter homologs) genes. Among the several signaling genes, Snf3 senses low levels of glucose, while Rgt2 senses high levels of glucose. Through the Snf3/Rgt2 pathway, yeast cells sense extracellular glucose levels and regulate the cell's glucose uptake. The last pathway involves the synthesis of cAMP (cyclic adenosine monophosphate), which controls the general cell cycle related to carbon metabolism and stress resistance.

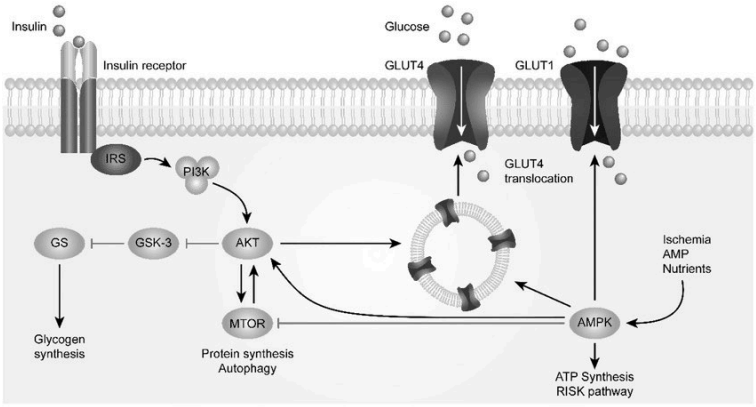


<Figure 7> Overview of glucose sensing and signaling pathways in yeast. (a) The main glucose repression (Snf1) pathway, (b) The Snf3/ Rgt2 pathway, (c) the Ras-cAMP pathway

Focusing on the first pathway, the Snf1 protein kinase in yeast is a homolog of AMPK protein kinase (adenosine-monophosphate-activated protein kinase) in eukaryotic cells, the key regulator for energy homeostasis. Thus, the understanding of the Snf1 kinase pathway can provide insight into how glucose uptake is stimulated by AMPK in the human body. Its energy homeostasis management is central to understanding blood glucose homeostasis, as the entering of glucose into cells triggers glycolysis for energy production. The metabolisms of tissues such as skeletal muscle and liver, and the beta-cells of the pancreas - which are critical to the development and management of diabetes type 2 - are regulated by AMPK and its energy homeostasis capacity.

4.3 Insulin signal transduction pathway

To achieve glucose homeostasis, Snf1 kinase activity (or AMPK in eukaryotic cells) needs to be stimulated, and glucose needs to be absorbed into the cell for glycolysis. The key element that enables glucose uptake is the well-known hormone insulin. Secreted from the pancreatic beta cells when increased blood glucose levels are detected, insulin binds to its receptors on the cells and allows the uptake of extracellular glucose. The numerous compartmentalized pathways of insulin signal transduction include the binding of insulin to the IR (insulin receptor), phosphorylation of IRS (insulin receptor substrates), insertion of glucose transporters into cell membranes, and ultimately cellular intake of glucose and initiation of glycolysis. Triggering enzymes to facilitate the insulin receptor signals would be a way to increase insulin sensitivity.



<Figure 8> Overview of AMPK on the insulin signal pathway. AMPK activation improves glucose uptake by phosphorylation of various substrates and activation of insulin receptors, along with the translocation of GLUT (Glucose transporter)

Overall, the study examines the catabolic mechanism of S. cerevisiae that controls glucose homeostasis through the use of sugars as sources of energy during glycolysis. In particular, the catalyst pathway of Snf1 protein kinase and insulin transduction pathway are identified as critical mechanisms behind managing extracellular blood glucose levels. Although the functions of insulin receptors, AMPK, and various proteins have been studied, certain processes of unknown kinases and glucose transport mechanisms that contribute to glucose homeostasis are unclear up to the present day. Further elaborate study on the process of signaling and activation of various enzymes will shed light on the full potential of cell coordination as a means of treating hyperglycemia. In addition, having understood the role of insulin signaling for glucose homeostasis, increasing the body's insulin sensitivity would be a feasible approach for diabetic treatments. Among the various treatments for type 2 diabetes, nutritional supplements can be employed to enhance insulin sensitivity and decrease insulin resistance. For instance, previous studies verify the medical uses of chromium. Chromodulin has the potential of escalating AMPK activity by stimulating the subunits of protein that sense, control, and manage extracellular glucose levels, along with the potential of aiding the insulin signaling pathway by activating insulin receptors. Once again, S. cerevisiae can be provided as the organic chromium producer that assists the body in building the chromodulin molecule. As a means of elevating insulin sensitivity to address hyperglycemia in type 2 diabetes, further research necessitates clinical trials.

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