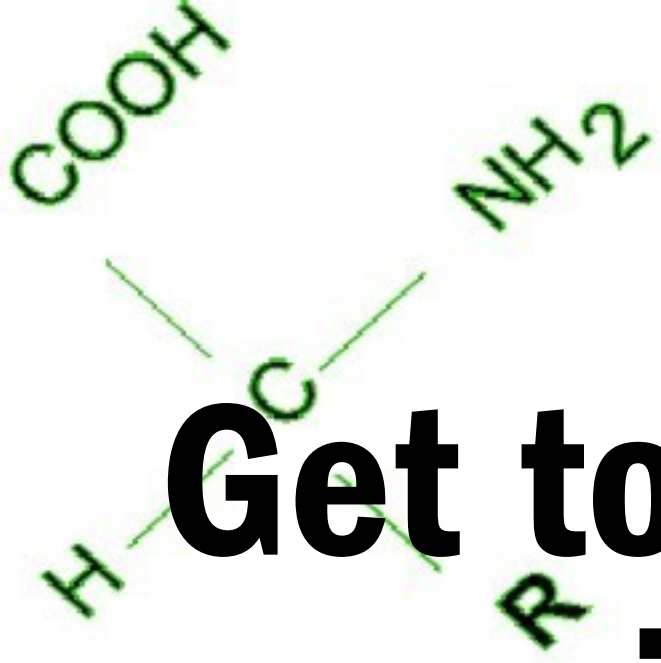

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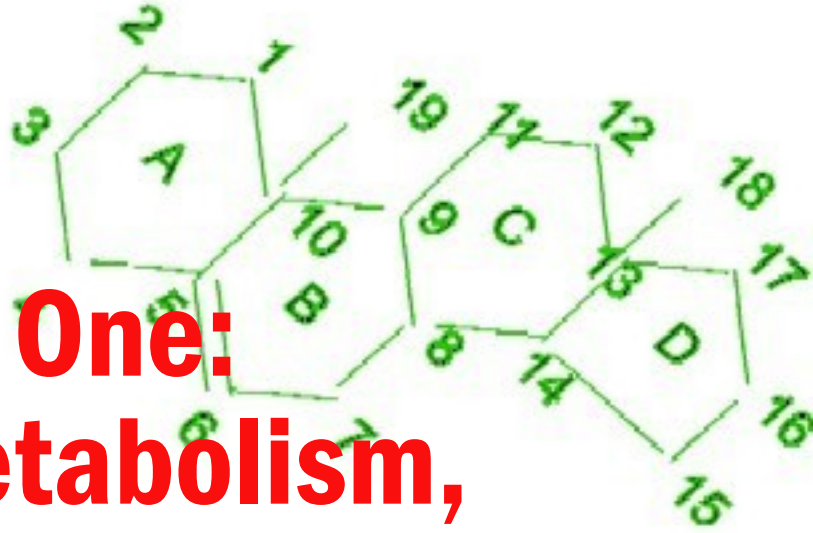

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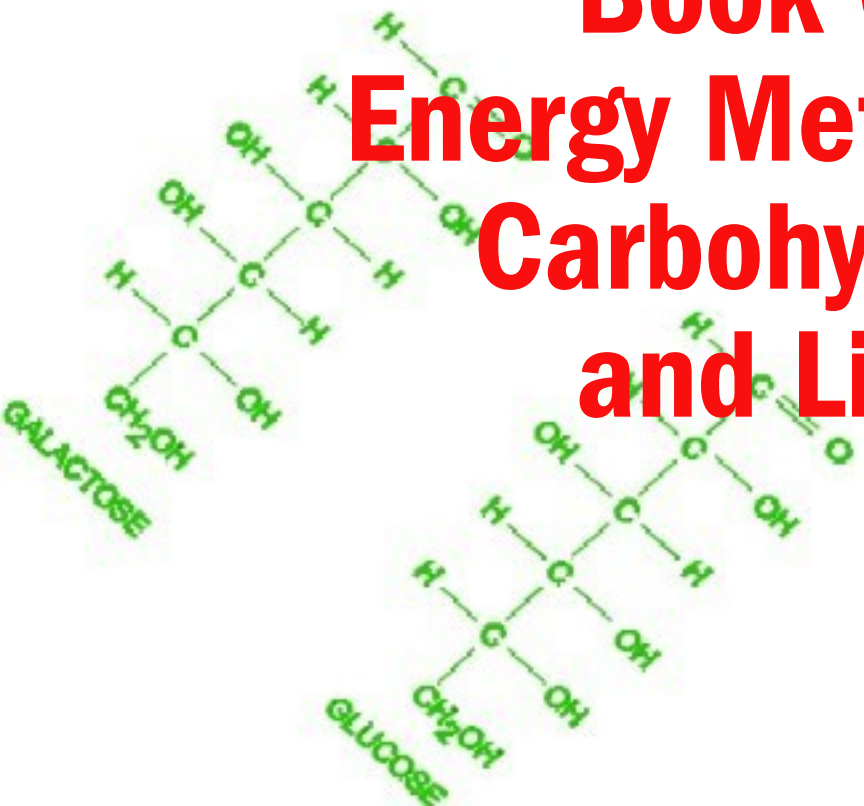

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Biochemistry is not difficult !!!

If you talk to the students in the years ahead of you in college most of them will tell you that biochemistry is a difficult subject. It's not !

Biochemistry studies the chemical reactions that occur in cells. Life, at the molecular level (and therefore biochemistry and molecular biology), is about *forming chemical bonds*. The things that living organisms do, such as grow and make "machines" which allow them to move, generate electrical impulses and perform other functions, all have one thing in common at the molecular level. They all involved atoms and/or small molecules being joined together by chemical bonds. When a house is being built bricks are "joined" together with cement. When structural components of cells and cell "machines" are being built the molecules that make up these structures are "joined" together by chemical bonds.

So, much of biochemistry involves studying the processes of forming chemical bonds between the molecules that make up the cells. For example, amino acid molecules are joined together by chemical bonds to make proteins which are the most important structural components of cells. Nucleotide molecules are joined together by chemical bonds to form DNA which is the stuff that the genes are made of.

In order to form chemical bonds energy is required. In this book we will look at the biochemistry of where this energy comes from. Now, it does not take a genius to work out that if it takes energy to form a chemical bond then a potentially good *source* of this energy is to break a different chemical bond. This is exactly how cells get the energy they need to form the chemical bonds between amino acids to form proteins, between nucleotides to form DNA and so on. The chemical bonds in certain molecules are sacrificed and the energy released when these bonds are broken is used to form other chemical bonds.

So, why does biochemistry seem so difficult? Unfortunately, the processes of forming or breaking chemical bonds usually occurs in a series of steps rather than in one single step. Furthermore, many of these reaction pathways are interlinked with each other. This all makes it difficult to break the subject of biochemistry down into discreet, individual sections that are easy to study and learn. Even when you do break the metabolic pathways down into manageable sizes you never get a full understanding of what is going on until you can see how the different pathways interact with each other. It is a bit like a jigsaw. You can only deal with one piece at a time but each piece in isolation does not make much of a picture.

Unfortunately, there does not seem to be an easy answer to this problem. Please, just carry on studying all the different pathways and structures individually. Don't get discouraged when you find it difficult to see the overall picture. When you have studied all the pieces (and there are not that many of them really!) you will eventually find that you will be able to fit them together to form the great picture that is the closest thing we have to understanding the meaning of life.

Whenever you get really confused as you plough through those enormous biochemistry textbooks or lost as you try and keep up with your biochemistry lectures ask yourself "What chemical bond is being formed or broken"? and you will find it much easier to follow what is going on.

I wish you an interesting time in your journey to understand what is known about how life works and of course good fortune in the exams you must pass to allow you to go on and pursue whatever career path you have set out on.

Paul M. Byrne

November 2008

How this book is organized

This book is different to other biochemistry books you have seen. It is small. It is not pages and pages of text and diagrams. Instead it is groups of short questions with short answers in short chapters. Each question highlights an important point or fact. As you follow the questions in sequence in each chapter you will be taken step by step through an important biochemical pathway and the associated chemical structures.

This book is not meant to be a substitute for biochemistry textbooks. In order to get a proper understanding and knowledge of any subject it is best to read a few different books and articles. However, many people find the detail in textbooks almost impossible to deal with when they start to study biochemistry. This book aims to give you a basic understanding of the important facts. Armed with this basic knowledge and understanding you will be better able to tackle those large and daunting textbooks.

You will also find this book useful for revision. If you know the information contained in these books you will be well able to deal with any questions in written exams, multiple choice or short answer questions and oral exams.

Let's summarize the contents of this book:

In the first section we review some basic concepts about chemical bonds and then we look at a molecule called ATP which is the source of much of the energy used to form chemical bonds in cells.

- In the second, third and fourth sections we look at how ATP is synthesized using energy from chemical bonds in some of the foods we eat. We look at how energy is extracted from the three basic groups of energy containing molecules (glucose and other carbohydrates, fatty acids and ketone bodies [which are derived from fatty acids] and finally, amino acids).

In the fifth section we look at how carbohydrates and fats are stored in the body as glycogen or triacylglycerols so that they can be used as energy sources when we are not eating. In the sixth section we look at NADPH which is an important molecule in the synthesis of the fatty acid components of triacylglycerols.

- In the seventh section we look at how these stores of food are converted back into the basic energy containing molecules so that the energy they contain can be used to synthesize ATP.

- In the eight section we look at some other important classes of lipid molecules. In section nine we see how basic energy containing molecules are extracted from the food we eat, absorbed and transported to the cells where they will be used. Finally, in section ten we take a closer look at how lipids are transported in the blood.

One of the most difficult aspects of learning biochemistry is the myriad of chemical structures you encounter. This book deliberately only includes a few of the more important ones. If you can draw the ones in this book you will know more than enough chemical structures to illustrate most points.

Please don’t spend your time trying to learn every chemical structure you come across in lectures and textbooks.

Finally, let me give you one of the great secrets to making learning easier. **REPETITION.**. Don’t read through the book once and expect to be able to remember and understand every detail. This is a relatively short book. Read it a few times. Every time you do you will learn and understand a little bit more. There is also repetition built into each chapter. Each section begins by introducing the topics to be covered and most chapters finish with some form of summary. Therefore by the time you have read the book once you will have covered all the important points three times. At the risk of repeating myself, let me remind you, that one of the big secrets to learning is **REPETITION** !

CHAPTER TWO

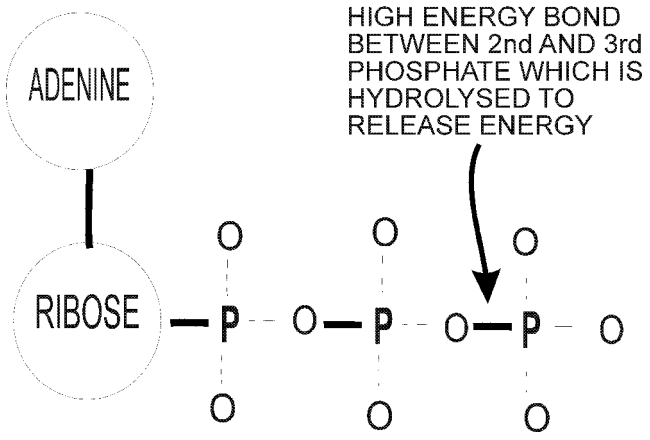
ADENOSINE TRIPHOSPHATE (ATP)

What molecule is most often used in cells as a source of energy for chemical bond formation ?

Adenosine triphosphate (ATP).

Which of the chemical bonds in ATP is usually broken to release energy ?

The bond that is *usually* broken is the one between the 2nd and 3rd phosphates (leading to the formation of adenosine diphosphate (ADP) and a free inorganic phosphate group (Pi)).



What is the problem with ATP and how is this problem overcome ?

ATP is very unstable and breaks down spontaneously at a very fast rate. Therefore it must be synthesized very close to the site where it is going to be used. This means you can't just eat neat ATP as it would all be broken down before it got to its site of action in the cells. This problem is overcome by synthesizing ATP inside cells, only when it is required, using the energy contained in the chemical bonds in certain energy rich molecules that we consume in our diet.

Name the two main molecules consumed in the diet as a source of energy ?

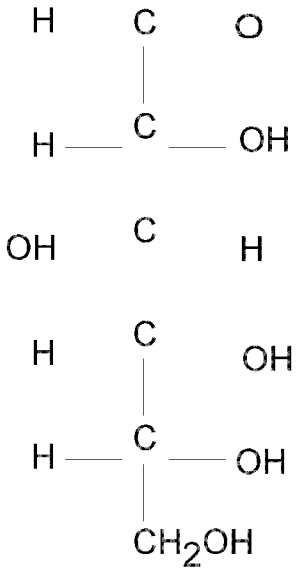
Carbohydrates (such as glucose) and fatty acids. Amino acids, can also be used to synthesize ATP when carbohydrates and fatty acids are scarce (during starvation, for example).

CHAPTER THREE

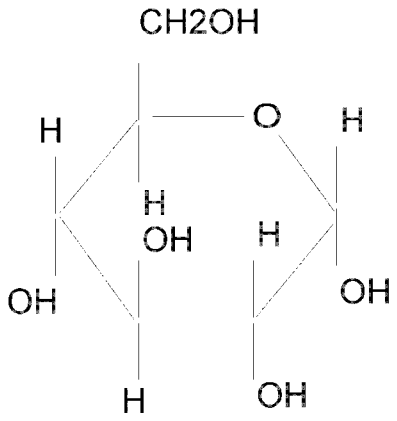
FIRST STAGE OF GLYCOLYSIS AND ENZYME INHIBITION

Draw the structure of glucose in its straight chain and cyclic forms.

GLUCOSE



OPEN CHAIN



CYCLIC FORM
BETA-D(+)-GLUCOSE

There are not many chemical structures that you have to be able to draw - but glucose is one of them.

What does the word glycolysis mean ?

Glycolysis means "splitting glucose". One of the first things discovered about glucose metabolism was that the six carbon structure was "split" into two three carbon structures (hence the name). Glycolysis is also called the Ebdemen-Meyerhoff pathway.

How many steps are there in the first stage of glycolysis ?

Four.

What is the first step in the first stage of glycolysis ?

Conversion of glucose into glucose-6-phosphate.

What enzymes catalyze this reaction ?

Hexokinase in muscle and glucokinase in the liver.

What other molecule is required in this reaction ?

ATP.

Does the answer to the last question strike you as odd ?

Yes, because glucose catabolism is supposed to make ATP and instead this first step uses ATP. However, you must use some ATP to "activate" the glucose before you can extract the energy from it.

What is the second step in glycolysis ?

Glucose-6-phosphate is converted into fructose-6-phosphate.

What is the third step in glycolysis ?

The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. ***This is an important step***.

What other molecule is required for this step ?

This step also uses a molecule of ATP.

What enzyme catalyzes this step ?

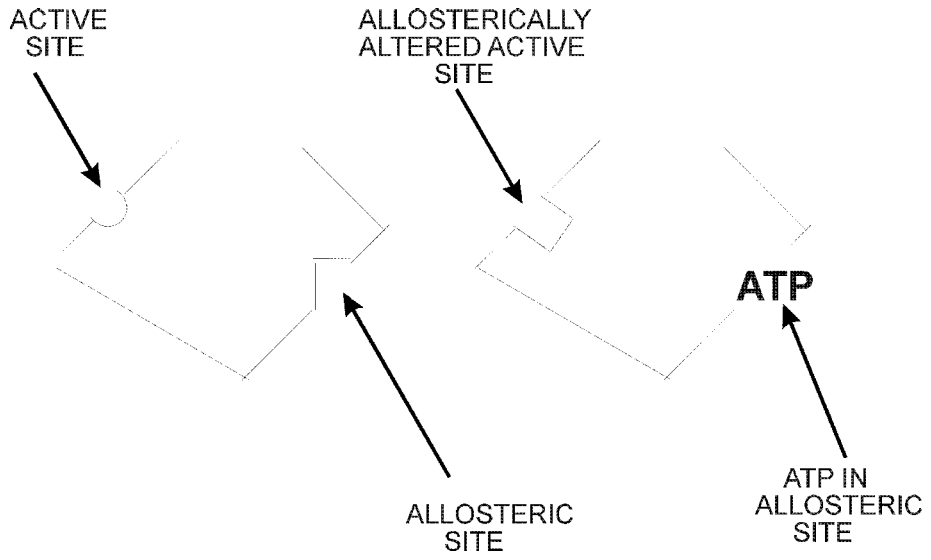
Phosphofructokinase (PFK) which is the rate limiting enzyme of glycolysis (and hence of ATP synthesis from glucose). Glycolysis as a whole will only proceed as fast as this enzyme can catalyze the formation of its product fructose-1,6-bisphosphate. (It's like a toll booth on a road. The number of cars entering and passing along the road is determined by the rate at which cars can get through the toll booth).

Name one way in which the activity of PFK can be controlled *?*

A high level of ATP will inhibit this enzyme. This makes sense because if there is lots of ATP around you do not need to be making more ATP.

How does ATP inhibit the enzyme PFK ?

It binds to a site on the enzyme called an allosteric site and this leads to *a change in the conformation* of the enzyme protein. This alters the shape of the active site (where the actual reaction takes place) which alters the activity of the enzyme which, in turn, alters the rate at which the reaction takes place. *This concept of allosteric control is an important on*e.



What is the inhibition of PFK by ATP an example of ?

It is an example of *feedback inhibition*, because a downstream product of an enzyme in a reaction chain "feeds back" to alter the activity of one of the enzymes in that reaction chain.

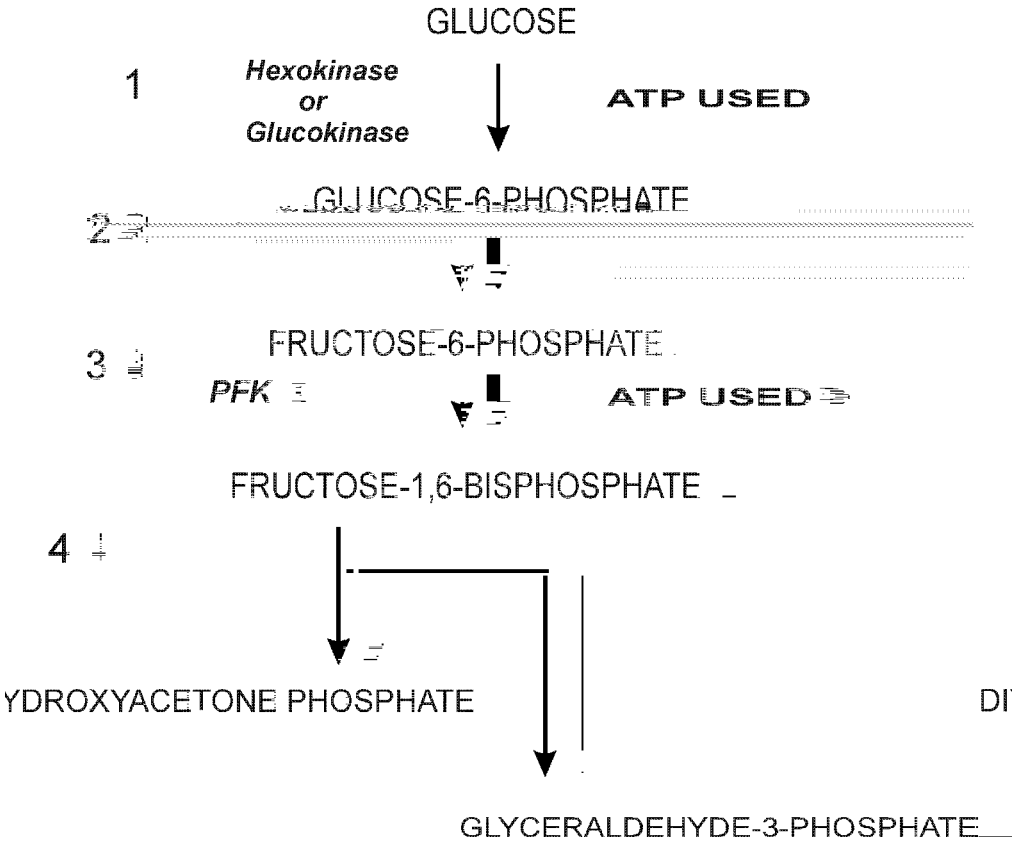
What is the fourth and final step in the first stage of glycolysis ?

The conversion of the six carbon fructose-1,6-bisphosphate into dihydroxyacetone phosphate (DHAP) and glyceraldehyde-3-phosphate (G-3-P). This reaction is catalyzed by the enzyme aldolase.

How many carbons do the products of this step have ?

DHAP and G-3-P are both three carbon compounds.

Draw a diagram of the first stage of the glycolysis pathway with the names of the important intermediates, enzymes and the sites where ATP is used.



CHAPTER TWENTY ONE

FATTY ACID STORAGE: TRIACYLGLYCEROL SYNTHESIS

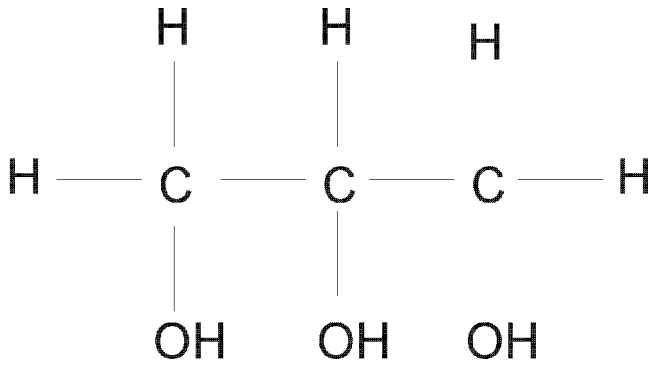
In what form are fatty acids stored in the body ?

Mainly in the form of triacylglycerols.

What are the constituent pats of a triacylglycerol molecule ?

Triacylglycerols consist of three fatty acids joined to a molecule of glycerol.

Draw the structure of glycerol.



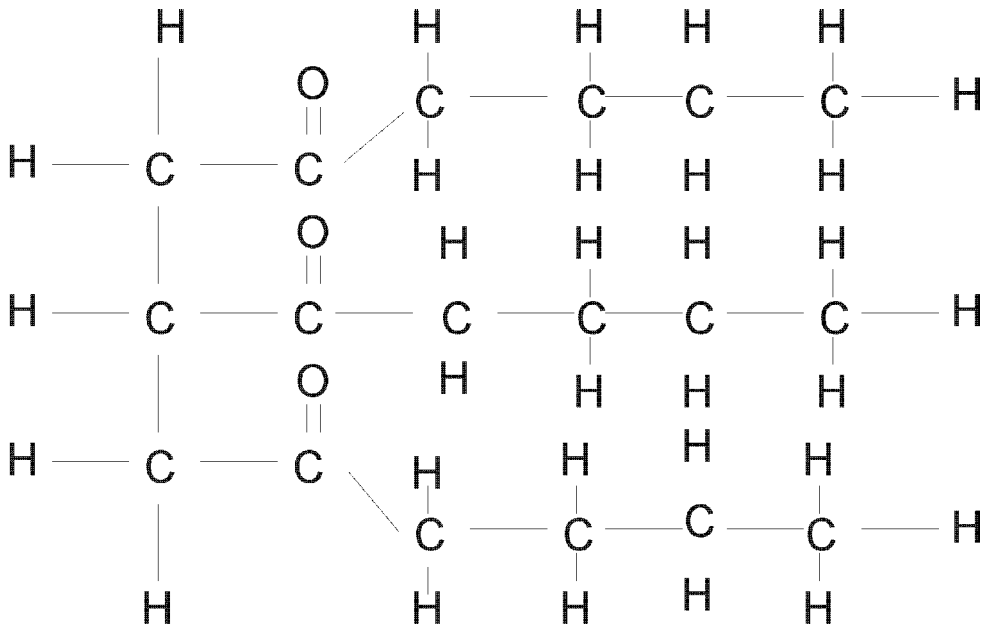
What kind of organic molecule is glycerol ?

It is an alcohol (i.e. it has hydroxyl (-OH) groups).

What are the chemical bonds between the carboxyl groups of the fatty acids and the hydroxyl groups of glycerol in a triacylglycerol called?

They are *ester* bonds (remember an acid and an alcohol forms an ester).

Draw the structure of a triacylglycerol molecule.



Note the glycerol molecule at the left of the diagram (as you look at it), the ester bonds between the carbons of the glycerol and the carboxyl carbons of the three fatty acid molecules and finally the three alkyl chains.

How is glycerol synthesized ?

Glucose is converted into glycerol by first converting it into dihydroxyacetone phosphate (in the glycolysis pathway). The DHAP is then converted into glycerol instead of glyceraldehyde-3-phosphate.

What are two advantages of triacylglycerol over glycogen as energy storage molecules ?

As mentioned in the chapter on beta oxidation, triacylglycerol contains more energy per gram than glycogen. Secondly, triacylglycerol is hydrophobic and so it is stored without water while glycogen is hydrated. This means that triacylglycerol takes up less space than glycogen.

CHAPTER TWENTY EIGHT

GLYCOGEN BREAKDOWN

What is the process by which glycogen is broken down in cells called ?

Glycogenolysis.

What is the important enzyme in glycogenolysis ?

Glycogen phosphorylase. This is a rate limiting enzyme (the reactions in the whole pathway can only proceed as fast as the rate at which the rate limiting enzyme catalyzes its reaction). Like many rate limiting enzymes glycogen phosphorylase is a target for various mechanisms of controlling the rate of the reaction pathway it is involved in.

What reaction does glycogen phosphorylase catalyze ?

It cleaves the bond between a glucose at the end of a glycogen chain and the glucose adjacent to it. The free glucose is then combined with a phosphate group to form glucose-1-phosphate.

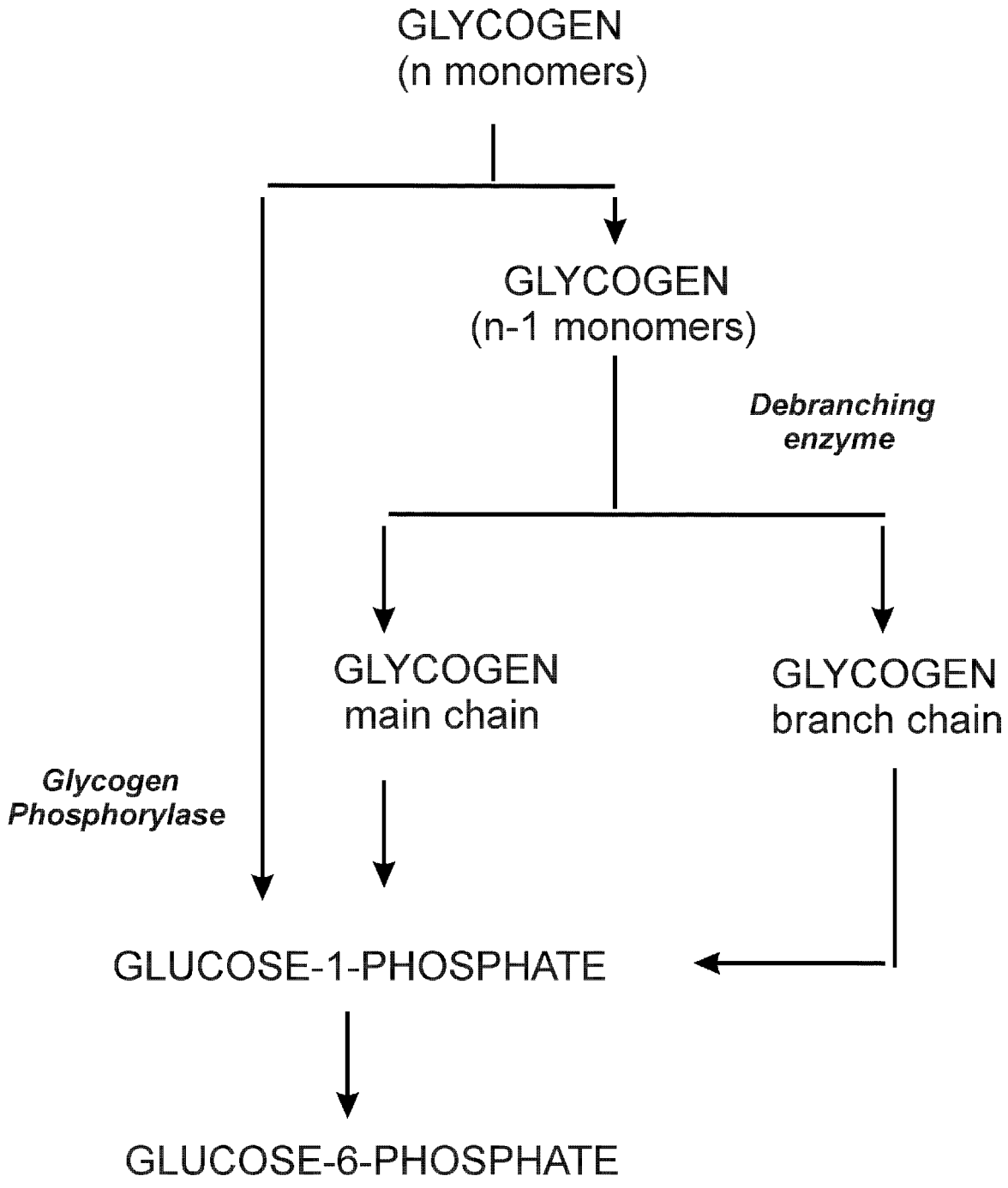
What happens when glycogenolysis reaches a branch point in a glycogen molecule ?

A second enzyme, the debranching enzyme, catalyzes the reactions necessary to remove the branch chain from the main chain. Then glycogen phosphorylase enzymes can act on oth bthe main chain and on the broken off branch chain to release more glucose molecules.

What happens to the glucose-1-phosphate molecules produced ?

The glucose-1-phosphate can then be converted back to glucose-6-phosphate and used for glycolysis.

Draw the important steps in glycogenolysis. Include the important enzyme(s).



CHAPTER FORTY FIVE

ENDOGENOUS LIPID TRANSPORT PATHWAY: VLDL AND IDL

You will notice that the endogenous pathway is very similar to the exogenous pathway

What is the average daily amount of triacylglycerol synthesized by the liver ?

25 to 50 grams per day.

What is the main lipoprotein type involved in transporting lipids from the liver to other cells ?

Very low density lipoproteins (VLDLs).

What is this pathway by which lipids are transported from the liver to other cells sometimes called ?

The endogenous pathway (as it transports the lipids that have been synthesized endogenously. This distinguishes it from the exogenous path which transports lipids consumed in the diet.)

What proportion of a VLDL particle is made up of triacylglycerol ?

50%. This is less than the proportion of triacylglycerol in chylomicrons.

What are the VLDL lipoproteins secreted by the liver called ?

Nascent VLDLs.

What are the major apoproteins found in nascent VLDLs ?

Apoprotein B-100 (chylomicrons have the smaller apo B-48 molecule) and small amounts of apo E and C-apoproteins.

What additional apoproteins do VLDLs acquire in the blood ?

They acquire more C-apoproteins and apo-E. The VLDLs are now mature VLDLs.

Where do VLDLs acquire these additional apoproteins from ?

They are transferred to the VLDLs from HDL lipoproteins.

How is some of the triacylglycerol removed from mature VLDLs in the blood ?

The extracellular lipoprotein lipase on the capillaries in muscle and adipose tissue removes some of the triacylglycerol from VLDLs by hydrolyzing it into monoacylglycerol and fatty acids.

What happens to the VLDLs as triacylglycerol is removed from the core ?

They become smaller.

What happens to the phospholipid, free cholesterol and C apoproteins that are shed from the VLDL coat as it becomes smaller ?

They are transferred to HDLs.

How else is triacylglycerol removed from VLDL ?

It is transferred to HDL particles in exchange for cholesterol ester. This process is similar to the triacylglycerol-cholesterol ester exchange that occurs in chylomicrons and again it is catalyzed by Cholesterol Ester Transfer Protein (CETP).

What are the resulting VLDL lipoproteins, which are now depleted of triacylglycerol and enriched with cholesterol ester, called ?

VLDL remnants.

What lipoproteins are found in VLDL remnants ?

Mainly Apo B100 and Apo E.

What happens to VLDL remnants ?

About half of the VLDL remnants, especially those that are larger and that still have multiple copies of apo-E, are taken up by the liver by an apo-E receptor dependent endocytosis similar to that of chylomicrons.

What are the smaller VLDL remnants called ?

The smaller VLDL remnants appear as a distinct band on centrifugation and are called Intermediate density lipoproteins or IDLs. (Some texts will use the terms IDL and VLDL remnants interchangeably. In this book the term IDL refers specifically to the smaller VLDL remnants which are converted to LDLs).

What happens to IDLs ?

They are further metabolized into low density lipoproteins (LDLs) - see next chapter.

What are the three functions of VLDLs ?

- The major function is to transport triacylglycerols synthesized in the liver to the extrahepatic cells such as muscle and adipose tissue.
- The second function is to transport cholesterol ester from the liver to the peripheral cells by means of LDLs (which some of the VLDLs are converted into).
- Finally, VLDLs are, like chylomicrons, involved in the pathway that transports cholesterol from peripheral cells to the liver.

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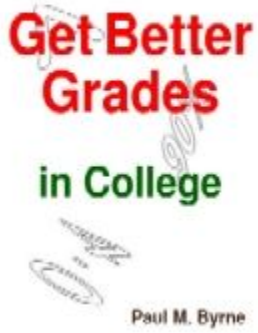

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