

The Effects of a Metabolic Block

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A Metabolic Block



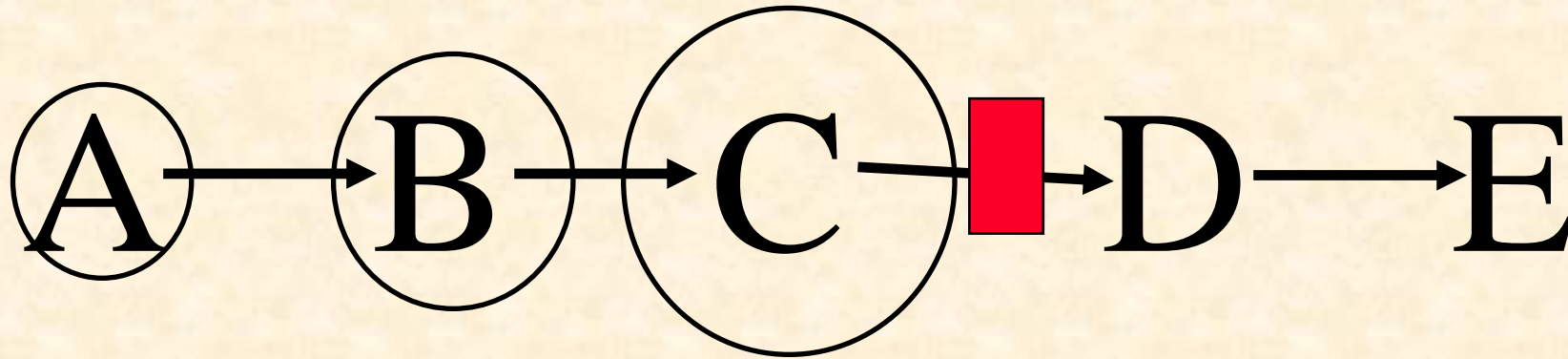
Consider a metabolic pathway where the flow of metabolites is from A to E. A loss of function of one of the steps in the pathway will lead to the accumulation of metabolites prior to the block and a depletion of the metabolites after the block.

The defect can be in an enzyme, a transport protein or a binding protein – the effect is generally the same.

The accumulation or depletion of metabolites may cause clinical symptoms. In some cases the clinical features may be a combination of both accumulation and depletion.

Measurement of accumulating or depleted metabolites can be used to diagnose the disorder and an understanding of the nature of these metabolites can help us understand the pathogenesis of the disease.

Accumulation



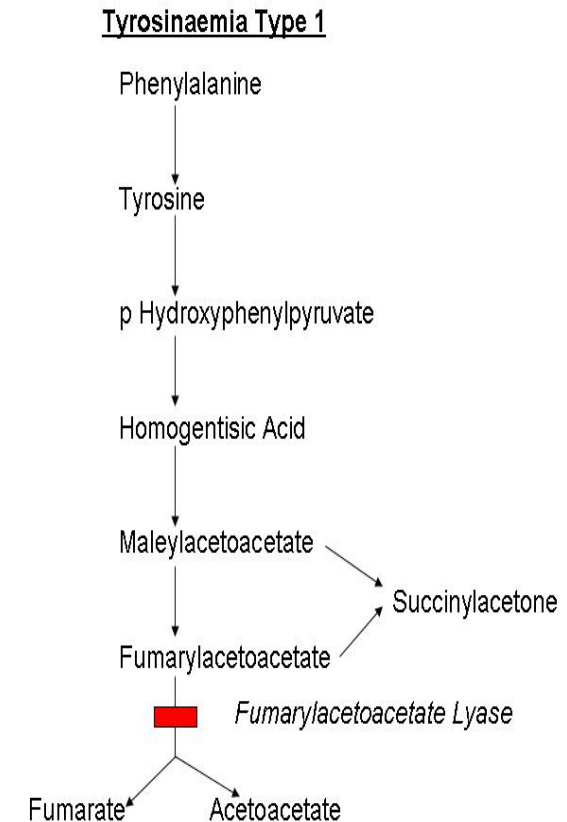
The metabolite immediately prior to the block accumulates (C). Further up the pathway other metabolites may accumulate (A & B) although usually, the further away from the block the metabolites are the less the accumulation. However, if one of the steps in these reactions is irreversible then no accumulation may occur prior to this step.

The level of accumulation is influenced by the severity of the defect and the rate of flux through the pathway. If the compounds entering the pathway come from the diet then it may be possible to modify the diet to reduce the rate of flux through the pathway and hence the level of metabolite accumulation. Alternatively if it is synthesised endogenously then inhibitors of biosynthesis could be used to reduce the rate of synthesis

Toxic Metabolites

Accumulation of a metabolite may of itself have no effect on the cells or body eg Histidinaemia. However it may have immediate effects on intracellular functions. Some accumulating metabolites are non-specifically toxic to cell proteins and nucleic acids.

An example of this is Tyrosinaemia type I where the accumulating metabolite, fumarylacetoacetate, actively binds to free thiol groups in proteins and glutathione. It can further convert non-enzymatically to succinylacetone which actively forms Schiff's bases with free amino groups of proteins. Not surprisingly in this disorder many enzymes are secondarily deficient.



Secondary Accumulation

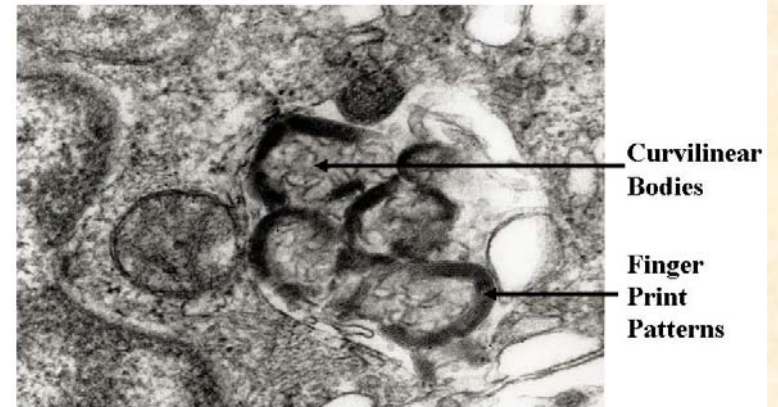
Other accumulating metabolites can specifically inhibit reactions, often because they are structurally similar to the substrates of reactions and can act as competitive inhibitors. The high plasma glycine concentrations seen in many organic acid disorders are believed to be due to inhibition by organic acids of reactions in the glycine cleavage enzyme multimeric complex.

As well as accumulating intracellularly, these metabolites can leak out of the cell and accumulate in the intercellular spaces and appear in the plasma, urine and cerebrospinal fluid. This can be convenient when one wants to diagnose the disorder but can mean that the metabolite may have effects on other organ systems.

Storage Diseases

If the molecule that accumulates is large then it may remain inside the cell and only small quantities appear in the blood or urine, probably released mainly when there is cell death. As a result the amount of stored material gradually increases with time. At a certain point the stored material starts to disrupt normal cell function. How it does this is not clear but in some cases it actually precipitates out and forms regular or irregular bodies that can be seen on histological examination eg Battens Disease (protein) and Glycogen Brancher Enzyme Defect. Eventually the cells become enlarged as can the whole tissue, leading to disruption of blood flow and drainage.

Electron microscopy of an eccrine gland in Battens Disease



Rates of Synthesis

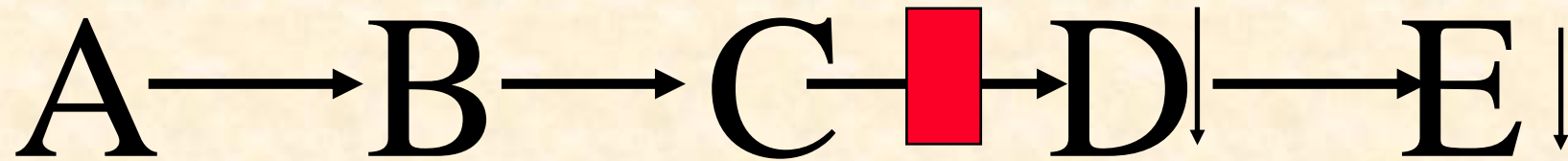
How fast the stored material accumulates depends on the degree of enzyme deficiency and the rate at which the cells take in or metabolise the starting substrate for the pathway and can vary from organ to organ.

If the rate of synthesis is low accumulation may be relatively modest and the cells may not be affected.

If the rate of synthesis is high then the organ may be the first one to show symptoms of the disorder. In general the higher the residual activity the later the symptoms develop as it takes longer for sufficient material to accumulate to a level where symptoms occur.

Where in the cell the material accumulates depends on where the block lies. Glycogen can accumulate in the glycogen storage diseases usually in the cytoplasm. However in one form of glycogen storage disease (Pompe Disease) the enzyme that is affected is in the lysosome so we only see lysosomal accumulation. The lysosome is a major site for the breakdown of many types of molecule so there are a whole group of diseases where accumulation occurs in this organelle.

Depletion



A metabolic block also results in the failure to produce compounds distal to the block (reduced concentrations of D & E in the diagram). Several metabolites will be depleted unless there are alternative pathways for their biosynthesis or if they can be obtained from dietary sources. Even then, if the biosynthetic pathway or the dietary sources are limited, under certain circumstances there may be still be significant depletion.

Whether this depletion has clinical effects obviously depends on whether the depleted metabolites have a function.

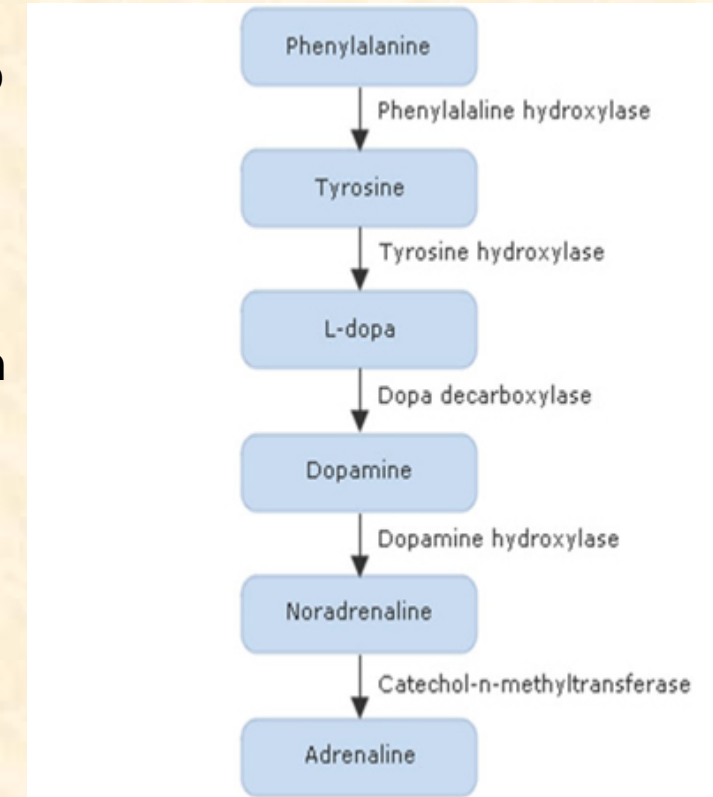
Accumulation vs Depletion

Alcaptonuria is due to a defect in the pathway for tyrosine degradation where there is a deficiency of homogentisic acid oxidase. Homogentisic acid accumulates and can cause joint problems but the reduced levels of the metabolites distal to the block do not cause symptoms.

However defects in biosynthetic pathways can obviously cause more problems with metabolite depletion.

L-DOPA is synthesised in the brain and a deficiency in the enzymes responsible for its biosynthesis can cause L-DOPA depletion and movement disorders (dystonia and choreoathetosis). Defects in the biosynthesis of hormones eg familial hypothyroidism also can obviously cause significant clinical problems. There are a whole group of disorders involved in the anaerobic and aerobic production of ATP for energy. Blocks in these pathways can produce ATP depletion within the mitochondrion or cytoplasm which results in a range of similar clinical symptoms.

Fortunately, some disorders can often be treated by supplementation of the depleted metabolite.



Factors that Modify Symptoms

We have seen how a metabolic block can lead to different clinical effects depending upon whether there is substrate accumulation or depletion. Within a disorder there is often quite a wide range of expression of symptoms both in terms of age of onset and the pattern and severity of symptoms.

We have seen how in the storage diseases this is often related to the level of enzyme activity and the rate of accumulation of stored material.

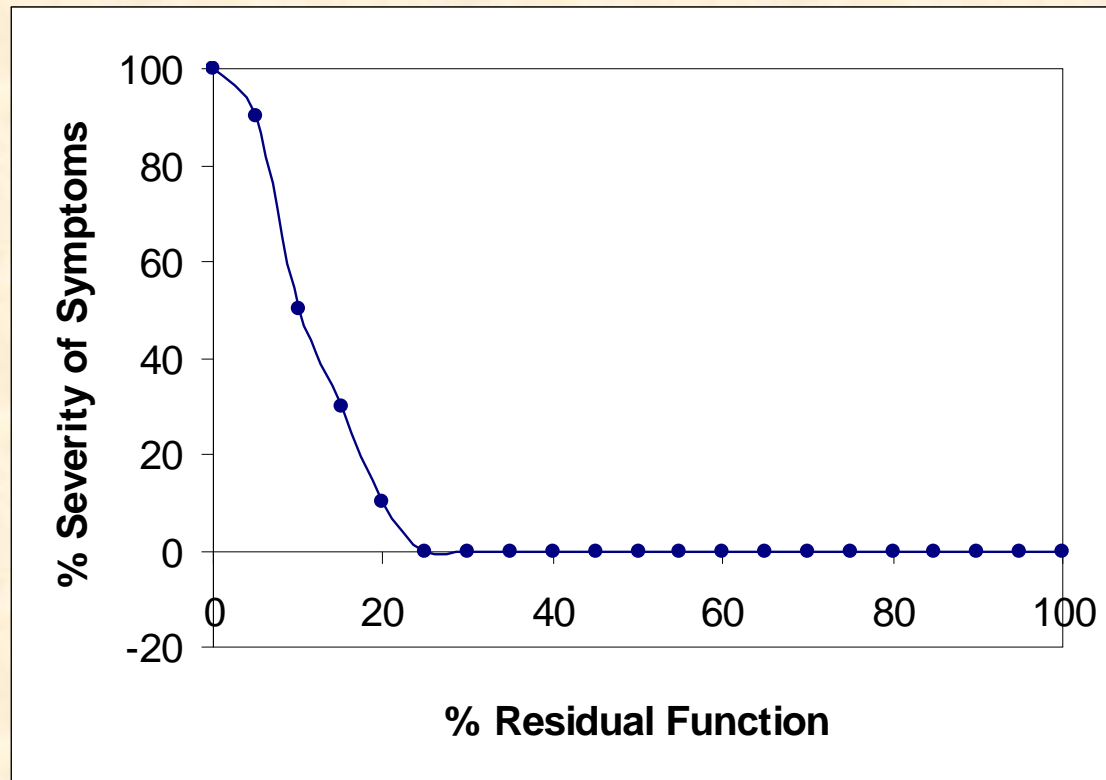
In many disorders it can be related to diet and to the level of intake of potentially harmful compounds (eg phenylalanine in Phenylketonuria) . Alternatively reduced dietary intake can cause further depletion influencing symptomatology (eg carnitine in disorders causing carnitine depletion).

Residual Activity and the Development of Symptoms

One might think that the level of clinical symptoms would vary linearly with the level residual activity but this is not necessarily the case.

In autosomal recessive disorders levels as low as 50% activity produce no symptoms although sometimes loading tests can show evidence of metabolite accumulation. In fact the level of residual activity at which symptoms first appear varies from disorder to disorder.

In many cases this reflects the balance between the levels of activity in the pathway. For every pathway one step will be the rate limiting step – usually the one with the lowest amount of enzyme relative to the others. Moderate reductions in activity in this enzyme will soon result in a dramatic drop in flux through the pathway. For steps in the pathway where the enzyme is well in excess the activity has to fall substantially before overall flux through the pathway changes dramatically.



An example of this is the lysosomal storage disease Metachromatic Leucodystrophy there exists a common polymorphism that gives activity of about 10% of normal but is not associated with symptoms. Symptoms only occur when one starts to fall below this value.

However some fatty acid oxidation defects present with symptoms with a high as 20% residual activity. Some tests measure the flux through a whole or part of a pathway in living cells whilst others measure the activity of individual functions in disrupted cells.

Because of the above factors the two results may not give the same values in terms of residual activity.

Modes of Inheritance

Autosomal dominant disorders are rare in inherited metabolic diseases - most being autosomal recessive or X-linked. This is mainly a reflection of the fact that in most metabolic pathways the proteins are well in excess and they have to be reduced to well below 50% activity before the flux through pathway is significantly reduced. In the few instances of dominant disorders symptoms occur because other factors come into play such as disturbances of regulatory functions or dietary factors eg the dominant forms of the porphyrias.

X-linked disorders can be purely recessive or dominant with partial penetrance. Males usually show similar expressivity and penetrance within a family and are more severely affected than females. The females show variability in expression of symptoms due to the random nature of X-chromosome inactivation making it difficult to predict the prognosis.

Mitochondria contain their own unique DNA and a group of disorders affecting respiratory chain function with mutations in this genome. They show maternal inheritance where only females can transmit the disease to both males and females.

Some Questions

Match the disorder to the whether accumulation or depletion is the primary cause of symptoms. The answers are on the next slide –no cheating!!

Accumulation Depletion

Tyrosinaemia type 1

Pompes Disease

Respiratory Chain Disorder

Metachromatic Leucodystrophy

Parkinson's Disease

Wilson's Disease

Alcaptonuria

The Answers

Click or Press Return to Reveal

	Accumulation	Depletion
Tyrosinaemia type 1	Y	
Pompe Disease	Y	
Respiratory Chain Disorder		Y
Metachromatic Leucodystrophy	Y	
Parkinson's Disease		Y
Wilson's Disease	Y	
Alcaptonuria	Y	