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Lysosomal Storage Disorders and Treatment

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ABSTRACT: The lysosomal system is the main intracellular mechanism for the catabolism of naturally occurring endogenous and exogenous macromolecules and the subsequent recycling of their constituent monomeric components. It also plays an important role in processing essential metabolites. A genetic defect in a protein responsible for maintaining the lysosomal system results in the accumulation within lysosomes of partially degraded molecules, the initial step in the process leading to lysosomal storage disorders. Lysosomal storage disorders are a group of genetic diseases, each with a broad spectrum of clinical presentation that ranges from attenuated to severe. The lysosomal storage disorders have been traditionally classified according to the biochemical composition of tissue deposits. Early diagnosis of lysosomal storage disorders before the onset of irreversible pathologies, will be a key factor in the development of effective therapies for many of these disorders**.** Prior to the advent of enzyme-replacement therapy, management options were mainly palliative although bone marrow transplantation was, and remains, a therapeutic approach for selected disorders. This review will examine the use of enzyme-replacement therapy and substrate-reduction therapy for particular LSD subtypes, and also briefly discuss emerging approaches that are currently in clinical trials (i.e., chaperone-mediated enzyme enhancement, stem cell and gene therapy).

Keywords:- Lysosomal storage disorders, Enzymes, Hunter syndrome, Glycogen degradation, GM_2 gangliosidosis, Kupffer cells.

INTRODUCTION

Lysosomal storage disorders are a diverse group of hereditary metabolic disorders that are typically inherited in an autosomal recessive manner. Approximately forty-five diseases have been described to date [1]. Lysosomal storage disorders are caused by a lack of enzymes that normally eliminate unwanted substances in the cells of the body. The enzymes are found in sac-like structures in cells called lysosomes. Lysosomes act as the "recycling center" of each cell, breaking down unwanted material into simple products for the cell to use to build new material. The deficiency of certain enzymes causes a buildup of the substance that the enzyme would normally eliminate and deposits accumulate in many cells of the body. Abnormal storage causes inefficient functioning and damage of the body's cells, which can lead to serious health problems.

HISTORY

Many of the diseases that we now know as lysosomal storage disorders were first described long before the

discovery of the lysosome in 1955 by de Duve[2]. As the structure and function of this organelle was defined and the different lysosomal proteins identified, the concept of lysosomal storage disorders evolved. The last decade has witnessed major advances in our understanding of the clinical, biochemical and genetical aspects of lysosomal storage diseases.

Tay-Sachs disease was the first of these disorders to be described, in 1881, followed by Gaucher disease in 1882 and Fabry disease in 1898. In the late 1950s and early 1960s, de Duve and colleagues, using cell fractionation techniques, cytological studies and biochemical analyses, identified and characterized the lysosome as a cellular organelle responsible for intracellular digestion and recycling of macromolecules. This was the scientific breakthrough that would lead to the understanding of the physiological basis of the Lysosomal Storage Diseases. Pompe disease was the first disease to be identified as an LSD in 1963, with L. Hers reporting the cause as a deficiency of α-glucosidase. Hers also suggested that other diseases, such as the mucopolysaccharide storage diseases, might be due to enzyme deficiencies.

EPIDEMIOLOGY

Lysosomal storage diseases affect mostly children and they often die at a young and unpredictable age, many within a few months or years of birth. Many other children die of this disease following years of suffering from various symptoms of their particular disorder. Individually, LSDs occur with incidences of less than 1:100.000, however, as a group the incidence is about 1:5000 - 1:10.000. Most of these disorders are autosomal recessively inherited, however a few are X-linked recessively inherited, such as Fabry disease and Hunter syndrome .

SYMPTOMS

The symptoms of lysosomal storage disease vary, depending on the particular disorder and other variables like the age of onset, and can be mild to severe. They can include developmental delay, movement disorders, seizures, dementia, deafness and/or blindness. Some people with Lysosomal storage disease have enlarged livers (hepatomegaly) and enlarged spleens (splenomegaly), pulmonary and cardiac problems, and bones that grow abnormally.

PATHOPHYSIOLOGY

Recent advances in molecular genetics have shifted the focus both in gene products and genes themselves. The defective genes in most of these genetic diseases have been isolated and characterized and the specific mutations identified. At the gene level, genetic heterogeneity is complex despite similar phenotypes, biochemistry, and enzyme defects.

CLASSIFICATION OF LYSOSOMAL STORAGE DISORDERS

The lysosomal storage disorders were divided into the following 5 groups:

A. Defects in glycan degradation
B. Defects in lipid degradation
C. Defects in protein degradation
D. Defects in lysosomal transporters
E. Defects in lysosomal trafficking

A. Defects in glycan degradation

The most common group of lysosomal storage disorders, represented by about 30 diseases, results from defects of glycan degradation. This group can be divided into the following four subgroups:

1. Defects in glycprotein degradation
2. Defects in glycolipid degradation
3. Defects in glycosaminoglycan degradation
4. Defect in glycogen degradation
5.

1. Defects in glycoprotein degradation

a) Sialidosis and galactosialidosis

Sialidosis is caused by the deficiency of hydrolase 1 and galactosialidosis is caused by the combined deficiency of β-galactosidase and neuraminidase.

The deficiency of hydrolase 1(sialidase) may be caused both by mutations in the sialidase gene [3] and in the gene encoding cathepsin A[4].Cathepsin A-deficiency causes combined sialidase and β-galactosidase deficiency due to its function in stabilising these two hydrolases[4].

The early infantile forms cause mental retardation, dysostis multiplex, hepatosplenomegaly and early death.

To determine if the patient has Galactosialidosis, the urine test should be followed by a blood test or skin biopsy. The blood or skin sample should show decreased amounts of the enzymes β- Galactosidase and Neuraminidase.

Treatment

Individuals with Galactosialidosis should have routine follow-up with Genetics, Ophthalmology, Cardiology, and other specialists as needed. Currently there is no cure to stop the progression of symptoms of Galactosialidosis, and treatment is aimed at addressing the individual problems as they arise.

b) Alpha-mannosidosis and beta- mannosidosis

Lysosomal alpha-mannosidase is a major exoglycosidase in the glycoprotein degradation pathway. A deficiency of this enzyme causes the lysosomal storage disease alpha-mannosidosis. Beta-mannosidosis is an autosomal recessive lysosomal storage disease resulting from a deficiency of the lysosomal enzyme beta-mannosidase.

Frequent clinical findings include recurrent bacterial infections, deafness, hepatomegaly and lenticular or corneal opacities.
Peripheral blood smears can reveal lymphocytes with vacuoles and neutrophils with some granules resembling Reilly bodies .

Treatment

Successful bone marrow transplantation in a child with a severe form of alpha-mannosidosis type I has been reported.

C) Schindler disease

Schindler disease results from the deficient activity of the enzyme alpha-*N*-acetylgalactosaminidase (alpha-galactosidase B), with the accumulation of sialylated-asialo-glycopeptide and oligosaccharide with alpha-*N* -acetylgalactosamilnyl residues. Two major types exist: type I and type II.
Type I or infantile-onset neuroaxonal dystrophy results in psychomotor retardation and myoclonic seizures are noted by age 3-4 years. Type II results in mild intellectual impairment with angiokeratoma corporis diffusum.
The diagnosis is established by abnormal urinary oligosaccharide and glycopeptide profiles and by the determination of the alpha-*N* -acetylgalactosaminidase activity in various sources.

Treatment

Treatment for Schindler disease focuses on its symptoms, since there is as yet no cure for the disease. Specialists such as a neurologist, eye doctor and geneticist will be involved in the individual's care. Physical and occupational therapy can help the individual with Type I disease maintain muscle movement and relieve discomfort.

2. Defects in glycolipid degradation

This group includes defects in:

- Degradation of G_{M1} ganglioside (G_{M1} gangliosidosis)
- Degradation of GM_2 ganglioside (GM_2 gangliosidosis)
- Degradation of sulfatide
- Degradation of globotriaosylceramide

Degradation of G_{M1} ganglioside

a) Gaucher's disease

Gaucher's disease is a sphingolipidosis resulting from glucocerebrosidase deficiency, causing deposition of glucocerebroside and related compounds.
Type I (non-neuronopathic) is the adult form of the disease that is particularly common among Ashkenazi Jews, among whom the incidence is reported to be as high as 1 in 850 [5]. Onset ranges from age 2 yr to late adulthood. Type I Gaucher's disease cause anemia, fatigue, lung impairment and kidney impairment.
Type II (acute neuronopathic) is rarest and residual enzyme activity in this type is lowest. Onset occurs during infancy. Type II Gaucher's disease cause liver enlargement and spleen enlargement.
Type III (subacute neuronopathic) falls between types I and II in incidence, enzyme activity and clinical severity. Type III Gaucher's disease cause progressive brain damage and seizures.
Diagnosis is by enzyme analysis of WBCs. Carriers are detected, and types are distinguished by mutation analysis.

Treatment

Enzyme replacement with placental or recombinant glucocerebrosidase is effective in types I and III; there is no treatment for type II disease. An oral treatment for Gaucher's disease (Zavesca, Miglustat, Actelion, UK) was licensed by the European authorities in April 2003 for those patients deemed unsuitable for enzyme replacement[6].

Degradation of GM_2 ganglioside

a) Tay-sachs disease

Gangliosides are complex sphingolipids present in the brain. There are 2 major forms, GM_1 and GM_2 . Tay-sachs disease is caused by the deficiency of hexosaminidase A results in accumulation of GM_2 in the brain.
Children develop progressive cognitive and motor deterioration resulting in seizures, mental retardation and paralysis.
Diagnosis is clinical and can be confirmed by enzyme assay.

Treatnent

β-hexosaminidase A from human urine infused intravenously in patients with Tay-Sachs disease results in 43% reduction in the elevated quantity of globoside in the circulation.

b) Sandhoff's disease

Sandhoff's disease is caused by the combined deficiency of hexosaminidase A and B .
Clinical manifestations include progressive cerebral degeneration beginning at 6 months accompanied by seizures, blindness, cherry-red macular spot and hyperacusis.
Diagnosis involves a test to measure enzyme activity of the two hexosaminidase enzymes. If the enzyme activity results indicate that there is no hexosaminidase activity, it means that the patient has Sandhoff disease. If, however, there is still B subunit activity, then this indicates that the patient might have Tay-Sachs disease.

Treatnent
Currently Sandhoff disease does not have any standard treatment and does not have a cure. However, a person suffering from the disease needs proper nutrition, hydration, and maintenance of clear airways. To reduce some symptoms that may occur with Sandhoff disease, the patient may take anticonvulsants to manage seizures or medications to treat respiratory infections.

Degradation of sulfatide
The inability to degrade sulfatides will cause accumulation of storage material in the brain and severe neurological symptoms, particularly by demyelination. Usually the disease begins at 3 months of age and soon progresses to severe mental and motor deterioration causing death before age of 2 years.

a) Krabbe's disease
Krabbe's disease (globoid cell leukodystrophy) is caused by an autosomal recessive galactocerebroside β-galactosidase deficiency.
It affects infants and is characterized by retardation, paralysis, blindness, deafness, and pseudobulbar palsy, progressing to death.
Diagnosis is by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.
Treatnent
Although there is no cure for Krabbe disease, bone marrow transplantation has been shown to benefit cases early in the course of the disease. Generally, treatment for the disorder is symptomatic and supportive. Physical therapy may help maintain or increase muscle tone and circulation. A recent study in the New England Journal of Medicine reports that cord blood transplants have been successful in stopping the disease as long as they are given before overt symptoms appear.

b) Metachromatic Leukodystrophy
Metachromatic leukodystrophy is a sphingolipidosis caused by arylsulfatase A deficiency which causes metachromatic lipids to accumulate in the white matter of the CNS, peripheral nerves, kidney, spleen, and other visceral organs; accumulation in the nervous system causes central and peripheral demyelination.
It produces blindness, hypotonia, paralysis , dementia, ataxia and depression.
Diagnosis is suggested clinically and by findings of decreased nerve conduction velocity; it isconfirmed by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.
Treatnent
Treatment options for metachromatic leukodystrophy are very limited. Bone marrow transplantation, when performed early in the course of the disease, has been used effectively on appropriate patients, but also poses some risk. Gene therapy research may eventually lead to a cure or treatment to slow the progression of MLD disease.

Degradation of globotriasylceeramide
The globotriasylceramide is a glycolipid that is predominantly found in the vascular endothelium and not in the nervous tissue.

a) Fabry's disease
Fabry's disease is a sphingolipidosis caused by deficiency of α-galactosidase A.
It produces angiokeratomas, acroparesthesias, corneal opacities, recurrent febrile episodes, and renal or heart failure.
Diagnosis is by assay of galactosidase activity—prenatally in amniocytes or chorionic villi and postnatally in serum or WBCs.
Treatment
Until recently, treatment of Fabry disease targeted the symptomatic effects.In 2001, two Enzyme Replacement Therapies (ERTs) were released: Agalsidase alpha (Replagal) and Agalsidase beta (Fabrazyme, Genzyme). The cost of these drugs is problematic (approximately $250,000 US a year/patient) and remains a barrier to many patients in some countries.

3. Defects in glycosaminoglycan degradation
Defect in the degradation of glycosaminoglycans characterises the disease group mucopolysaccharidosis (MPS).

a) Mucopolysaccharidoses
MPSs result from abnormal degradation of glycosaminoglycans such as dermatan sulfate, keratan sulfate, heparan sulfate and chondroitin sulfate resulting in organ accumulation and eventual dysfunction. Alpha-L-iduronidase, which cleaves terminal L-iduronic acid residues from both dermatan and heparan sulfate, is deficient.

Clinical presentations
MPS type I includes Hurler, Hurler-Scheie and Scheie syndromes.

- MPS type I H (Hurler syndrome)
  - Most children with Hurler syndrome have recurring upper respiratory tract and ear infections, noisy breathing, and persistent copious nasal discharge.
- MPS type I H/S
  - This form is intermediate between the Hurler syndrome and Scheie syndrome.
  - It is characterized by progressive somatic involvement, with little or no intellectual deterioration.
- MPS type I S

  - Joints are stiffened, and the skeletal abnormalities are most pronounced in the hands, with claw hand deformity.
- MPS type II (Hunter syndrome)
  - Iduronate-2 sulfatase is deficient.
  - Mortality results from cardiorespiratory dysfunction
- MPS type III (Sanfilippo syndrome)
  - Deficiencies in heparan *N* -sulfatase (type A), alpha *N* -acetylglucosaminidase (type B), acetyl CoA:alpha-glucosaminide acetyltransferase (type C), and *N* -acetylglucosamine 6-sulfatase (type D) can occur. All 4 enzymes are required for the degradation of heparan sulfate. All 4 forms have autosomal recessive inheritance.
  - The distinguishing feature is severe central nervous system degeneration but only mild somatic disease.
- MPS type IV (Morquio syndrome)
  - MPS IV results from defective degradation of keratan sulfate.
- MPS type VI (Maroteaux-Lamy syndrome)
  - A deficiency in arylsulfatase B (ie, *N* -acetylgalactosamine 4-sulfatase) occurs.
  - Death typically occurs from heart failure.
- MPS type VII (Sly syndrome)
  - MPS VII is caused by a deficiency in beta-glucuronidase,
  - Features include dysmorphic facies, protruding sternum, hepatosplenomegaly,

Simple enzyme assays are available for the diagnosis of MPS from fibroblast, leukocyte or serum samples.

Treatment

Exogenous enzyme replacement therapy with recombinant human alpha-L-iduronidase (Aldurazyme).Gene therapy has shown promising results on animal models.

4) Defects in glycogen degradation

The defective degradation of glycogen in the lysosomes is caused by the lack of a single enzyme, lysosomal acid alpha-glucosidase resulting in glycogen storage disease type II (Pompe disease)[7].The classic infantile form of the disease causes cardiomegaly, hypotonia, hepatomegaly and death before 2 years of age due to cardiorespiratory failure.

B. Defects in lipid degradation

The defects in lipid degradation involve the two steps degradation of sphingomyelin to sphingosine and the ester hydrolysis of triglycerides and cholesteryl esters.

a)Niemann-pick disease

Niemann-Pick disease is a rare inherited autosomal recessive lipid-storage disease. Type A Niemann-Pick disease is a severe neurodegenerative disorder of infancy that leads to death by age 3 years, whereas type B disease has a later age at onset, little or no neurologic involvement, and survival of most patients into adulthood.

Niemann–Pick type C disease is caused by deficiency of the NPC-1 protein(Table3.c) involved in cholesterol trafficking. Patients accumulate non-esterified cholesterol as well as sphingolipids. These lipids are thought to play an important role in the formation of lipid rafts which have been shown to be critical for insulin receptor signalling in hepatocytes [8]

Patients develop growth delay,brain related problems and hepatosplenomegaly.

Prenatal diagnosis of Niemann-Pick disease types A and B is routinely accomplished by sphingomyelinase assay. For Niemann-Pick disease type C, demonstration of abnormal intracellular cholesterol trafficking is a complex procedure, and mutational analysis (ie, *NPC1* or *NPC2/HE1* gene) can be feasible.

Treatment

At present no specific treatment is available for patients with any Niemann-Pick disease subtypes and treatment is symptomatic. Orthotopic liver transplantation in an infant with type A disease and amniotic cell transplantation in several patients with type B disease have been attempted with little or no success. Bone marrow transplantation in a patient with Niemann-Pick disease type B was successful in reducing spleen and liver volumes.

b) Wolman disease and cholesteryl storage disease

Wolman disease is caused by genetic defects of lysosomal acid lipase that leave no residual enzyme activity. Wolman disease is also called primary familial xanthomatosis with involvement and calcification of the adrenal glands.

Wolman disease is characterized by severe diarrhea and malnutrition leading to death during infancy.

Diagnosis shows an enlarged liver with decreased density and heavily calcified adrenal glands.Ultrasonography reveals an enlarged liver with normal echogenicity and adrenal calcification.

Treatment

In mouse gene therapy, in the form of gene transfer via intravenously administered adenovirus, has been used to correct deficiency states, such as Wolman disease and cholesteryl ester storage disease.

C. Defects in protein degradation

Diseases caused by the deficiency of lysosomal proteases are rare among the lysosomal storage disorders. Three disorders caused by the lack of cathepsin K(Table1.a), tripeptidyl-peptidase(Table1.b) and palmitoyl-protein thioesterase(Table1.c) are so far the only proteinase deficiencies reported.

D. Defects in lysosomal transporters

After lysosomal hydrolyses of macromolecules in the lysosomes the building blocks as monosaccharides and amino acids are transported through the lysosomal membrane into cytosol.

Mutations in the sialic acid transporter (sialin) cause sialic acid storage disease [9].The children usually die before the age of 1 year. The juvenile/adult form of the disease is called Salla disease(Table2.a) due to its prevalence in the Salla region of Finland.

Defiency of the cystine transporter (cystinosin) results in the storage disorder cystinosis(Table2.b). The affected children are usually born healthy and develop signs of kidney disease before age of 1 year[10].

TABLE-1 DEFECTS IN PROTEIN DEGRADATION

Chromosomal protein defect localization	**Disorder**
a) Cathepsin K b) Tripeptidyl peptidase c)Palmitoyl-protein thioesterase	Pycnodystostosis Ceroide lipofuscinosis 2 Ceroide lipofuscinosis 1

TABLE-2 DEFECTS IN LYSOSOMAL TRANSPORTERS

Lysosomal transporter	**Disorder**
a) Sialin (sialic acid transport) b) Cystinosin (cystin transport)	Salla disease Cystinosis

TABLE-3 DEFECTS IN TRAFFICKING

Lysosomal trafficking proteins	**Disorder**
a)Phosphotransferaseγ-subunit	Mucolipidosis III (I-cell)
b)Mucolipin-1(cation channel)	Mucolipidosis IV
c) NPC1	Niemann Pick type C
d)CLN3	Ceroid lipofuscinosis
e)CLN 6	Ceroid lipofuscinosis 6
f)CLN 8	Ceroid lipofuscinosis 8
g)MYOV	Griscelli Type 1
h)RAB27A	Griscelli Type 2
i)Melanophilin	Griscelli Type 3
j)AP3 β-subunit	Hermansky Pudliak 2

E. Defects in trafficking

Deficiencies in trafficking have recently been recognised to cause several lysosomal disorders. The deficient proteins may not be directly linked to a lysosomal location, but may be present in the trafficking route of lysosomal proteins from endoplasmic reticulum (ER) to the lysosomes. Thus, both cytosolic proteins as well as ER/Golgi/endosome/lysosome localised proteins involved in trafficking may cause lysosomal storage disorders.

CENTRAL NERVOUS SYSTEM THERAPY FOR LYSOSOMAL STORAGE DISORDERS

The blood–brain barrier has represented a significant impediment to developing therapeutic approaches to treat brain disease, but novel approaches—including enzyme replacement, small-molecule, gene, and cell-based therapies—have given children afflicted by these conditions and those who care for them hope for the future.

Enzyme replacement therapy

ERT were performed by infusing normal human enzymes into individuals who had a variety of LSDs. Enzyme replacement therapy was first developed for Gaucher disease. Brady and colleagues initially used an enzyme preparation purified from human placenta [11]. ERT for non-neuronopathic Gaucher disease has been a great success [12]. It is highly effective in treating visceral disease and, although there are occasional patients on ERT who suffer ongoing skeletal complications, for the most part the bone disease responds well and patients have a much improved quality of life (QoL) [13].This success led to attempts to use ERT in other LSDs[14].

Enzyme delivery across the blood brain barrier

Bulky recombinant enzymes used for treatment of LSDs are widely considered to be unable to penetrate across the BBB, limiting their utility for treating disorders characterized by brain pathology.Intravenously injecteda-mannosidase, a lysosomal enzyme, was able to enter the brain immediately after barrier opening and was incorporatedinto neuronal lysozymes within the 1st day after infusion.

Intrathecal and intraventricular enzyme delivery

Direct infusion of enzymes via an intrathecal or intraventricular route is another potential method for by passing the BBB.

Bonemarrow,hematopoietic stem cell and umbilical cord blood transplantation

Allogenic BMT, HSCT and more recently umbilicalcord blood transplantation have been mainstays of therapeutic intervention for many LSDs .

Small molecule therapies-substrate reduction and chaperones

Substrate reduction therapy with *N*butyldeoxynojirimycin(miglustat) may also benefit patients who have neurological involvement, because it has the ability to cross the BBB. Proof of principle of this approach was demonstrated in an *in vitro* model of Gaucher disease [15]. Subsequent studies in mouse models of Tay–Sachs [16], Sandhoff [17], Fabry [18] and G_{M1} gangliosidosis [19]have demonstrated the general utility of this drug in glycosphingolipid storage disorders.

In some cases, LSDs are due to mutations which cause instability of the enzyme [20]One approach to therapy in these cases is to use small molecules that enhance folding or facilitate stabilization of the active site of the enzyme, so called chaperone therapy [21] .

In contrast to substrate reduction therapy, chaperone therapy is designed to enhance innate enzyme activity by restoring the shape of misfolded lysosomal enzymes.

Gene therapy

The brain has limited capacity for regeneration, so any technique employing direct intraparenchymal or intraventricularinjection must minimize direct damage to brain tissue while delivering the therapeutic vector as widely as possible. Because only a fraction of normal enzyme activity would be expected to result in clinical benefit, the experimental technique of gene therapy may offer cures in the future [22].

Cell based therapies

Cell-based therapies are also attractive candidates for treatinglysosomal disorders associated with significant brain disease.

TARGETTING OF LYSOSOMAL STORAGE DISORDERS

Acid hydrolase enzymes destined for targeting to the lysosomal matrix are first synthesized in the rough endoplasmic reticulum (fig.1). A M6P moiety is added in the cis-Golgi network. These “tagged” enzymes bind to receptors located in the membrane of vesicles that bud from the trans-Golgi network and fuse with lysosomes releasing the “tagged” enzyme into the lysosomal matrix. A proportion of enzymes destined for lysosomes are execreted and reenter the cell via

M6P receptors located on the outer cell membrane. This extrinsic pathway is the basis for exogenous enzyme replacement therapy.

Targeting exogenous enzymes

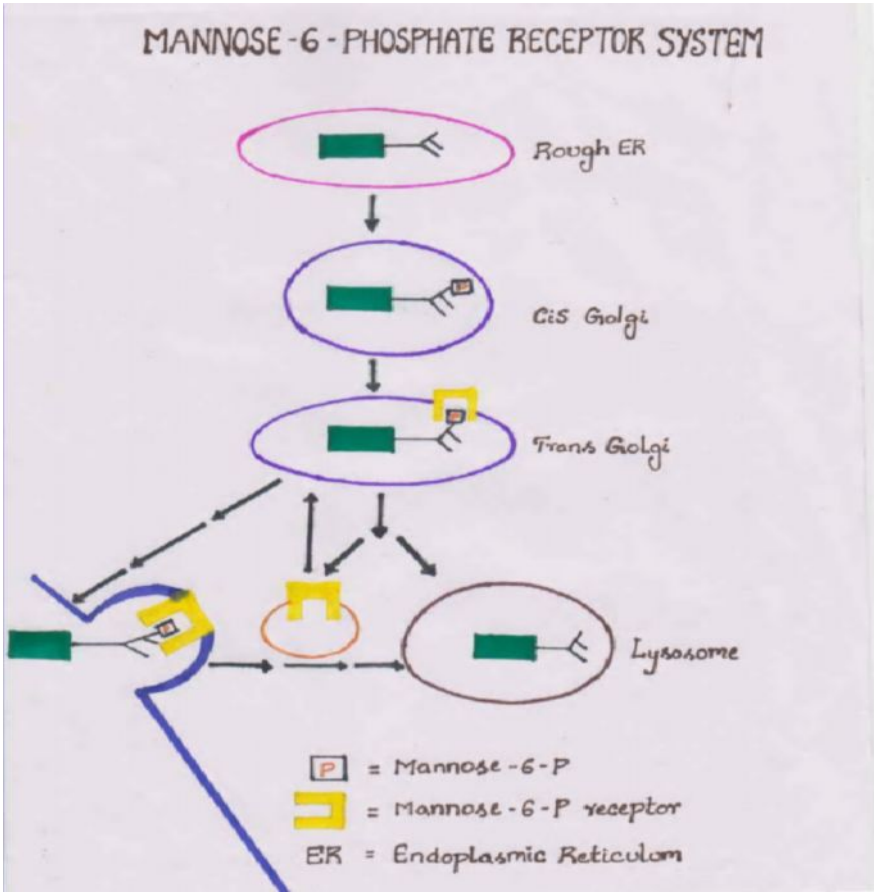
It was aimed to specifically target the cells in which the accumulating toxic materials accumulate. Direct the major portion, if not all of the exogenous enzyme, to the storage cells - Hepatocytes have a galactose lectin on their membranes, any glycoprotein with a terminal molecules of galactose will usually be preferentially endocytosed by these cells e.g. glucocerebrosidase, removing terminal molecules of sialic acid there by exposing additional molecules of galactose further increases its delivery to cells. Removal of galactose from sialidase-treated glucocerebrosidase increased the delivery of this enzyme to Kupffer cells.

CURRENT AND FUTURE DEVELOPMENTS

Although the cumulative incidence of the various LSD subtypes is relatively high, individually they are infrequent to rare clinical entities. Thus, the LSDs are viewed by drug regulatory agencies as 'orphan' disorders, and there exists appropriate legislation to promote venture capital investment to develop drugs for these indications. A major challenge in the development of treatment for these conditions lies with the fact that in the majority of conditions there is severe neurologic involvement, and in certain cases the cellular insult may be present, even prenatally. Thus,concurrent with efforts to introduce novel therapies progress will have to occur in the ways patients are identified, to permit diagnosis at an earlier stage of their disease.

In summary, the broadening spectrum of current and potential avenues of treatment for the LSDs raises the prospects of a brighter future for afflicted families.

Fig.No:- 1. Mannose-6-phosphate receptor system



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