Biochemical and Molecular Basis of Single Gene Disorder.

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Enzyme.

- Substance acting as a catalyst in living organisms,
- Regulating the rate at which chemical reactions proceed without itself being altered in the process.

- Biological processes that occur within all living organisms are chemical reactions, and most are regulated by enzymes.

Enzyme contd…

- Catalyze all aspects of cell metabolism.
- e.g. digestion of food, conservation and transformation of chemical energy.

- Many inherited human diseases, such as albinism and phenylketonuria, result from deficiency of a particular enzyme.

Composition of enzyme.

- Composed of 1 or more amino acid chains called polypeptide chains.

- If subjected to changes, such as fluctuations in temp. or pH, the protein structure will be denatured and will lose its enzymatic ability.

Cofactor.

- Bound to some enzymes is an additional chemical component called a cofactor, which is a direct participant in the catalytic event and thus is required for enzymatic activity.
- A cofactor may be either a coenzyme→an organic molecule, such as a vitamin or an inorganic metal ion.
- Some enzymes require both.

Examples of enzymes.

- Digestive enzymes of animals→ → →
- Pepsin is a critical component of gastric juices, helping to break down food particles in the stomach.
- Amylase, which is present in saliva, converts starch into sugar, helping to initiate digestion.

Contd…

- Thrombin is used to promote wound healing.
- Lysozyme destroys cell walls and is used to kill bacteria.
- Catalase brings about the reaction by which hydrogen peroxide is decomposed to water and oxygen.
- Also protects cellular organelles and tissues from damage by peroxide, which is continuously produced by metabolic reactions.

Enzymes work.

- By binding to reactant molecules and holding them in such a way that the chemical bond breaking and bond forming processes take place more readily.
- With the catalyst, the activation energy is lower than without.

Contd…

- Catalyze all kinds of chemical reactions that are involved in:

✓ Growth,

✓ Blood coagulation,

✓ Healing,

✓ Diseases,

Contd…

- ✓ Breathing,
- ✓ Digestion,
- ✓ Reproduction,
- ✓ Many other biological activities.

What is an enzyme disorder?

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What is an enzyme disorder?

- If an enzyme is missing:

✓→Blockage of pathway →
✓→Deficiency in formation of final product →
✓→Disease.

Contd…

- If an enzyme has low activity:

✓→ The subsequent accumulation of the enzyme's substrate, which may be toxic at high levels.

Diseases caused by enzymes disorders...

- Familial hypercholesterolemia,
- Gaucher disease,
- Hunter syndrome,
- Krabbe disease,
- Maple syrup urine disease,

Contd…

- Metachromatic leukodystrophy,
- Mitochondrial encephalopathy,
- Lactic acidosis,
- Stroke like episodes (MELAS).
- Niemann Pick.

Can enzymes be mutated?

- **Mutations** in **enzymes** →
- ✓ →Serious or fatal disorders in humans,
- ✓ →Inherited abnormalities in the DNA of the affected individual.

- ✓ May be just as a single abnormal amino acid residue at a specific position in an enzyme encoded by a mutated gene.

Mucopolysaccharidoses.

- Group of inherited diseases.
- Defective or missing enzyme → Accumulation of complex sugar molecules in cells.
- Progressive damage to the heart, bones, joints, respiratory system and central nervous system.

Contd…

- Disease may not be apparent at birth, signs and symptoms develop with age as more cells become damaged.

Lysosomal storage disorders.

- Group of approximately 50 inherited disorders.

- Occur when a missing enzyme results in the body's inability to recycle cellular waste.

LSD Contd…

- Severity of the disorder depends on the type and amount of cellular debris that accumulates, but almost all disorders are progressive.

- Many of these children die in infancy or early childhood.

Signs & symptoms of LSD.

- Affected individuals often have:
- ✓ Intellectual and developmental disabilities,
- ✓ Cloudy corneas,
- ✓ Short stature, Stiff joints,
- ✓ Incontinence,

Contd…

- ✓ Speech and hearing impairment,
- ✓ Chronic runny nose,
- ✓ Hernia,
- ✓ Heart disease,

Contd…

- ✓ Hyperactivity,
- ✓ Depression,
- ✓ Pain and a dramatically shortened life span.

Nieman-Pick Disease.

- Group of inherited metabolic disorders known as lipid storage disorders.
- Patients lack a critical enzyme necessary to metabolize fatty substances(lipids) in the body

- →Harmful quantities of lipids accumulation in the spleen, liver, lungs, bone marrow & brain.

Symptoms of NPD.

- ✓ Lack of muscle coordination,
- ✓ Brain degeneration,
- ✓ Learning problems,
- ✓ Loss of muscle tone,

Contd…

- ✓ Increased sensitivity to touch,
- ✓ Spasticity,
- ✓ Feeding and swallowing difficulties,
- ✓ Slurred speech,
- ✓ An enlarged liver and spleen.

Types of NPD.

- Type A,
- Type B,
- Type C,
- Type D.

Type A..

- The most common type which occurs in infants.

- Children rarely live beyond 18 months.

Type B.

- Involves an enlarged liver and spleen, which usually occurs in the pre-teen years, but the brain is not affected.

Types C & D.

- May appear early in life or develop later in the teens.
- Individuals may have only moderate enlargement of the spleen and liver,
- But brain damage may be extensive and cause→

✓ Inability to look up and down,

✓ Difficulty in walking and swallowing,

✓ Progressive loss of vision & hearing.

Phenylketonuria (PKU).

- **Deficiency** of the **enzyme** Phenylalanine hydroxylase (PAH) → High levels of phenylalanine in the blood.

- Intellectual disability results if the condition is not recognized.

Glycogen storage diseases.

- Problems with sugar storage →

✓ Low blood sugar levels,

✓ Muscle pain,

✓ Weakness.

Transmission Patterns of Single Gene Disorders.

- **Autosomal dominent disorders:**

✓ Charracterised by expression in heterozygous state.

✓ They affect males and females equally.

✓ Both sexes can transmit the disorder.

Contd…

- ✓ Enzyme proteins are not affected instead receptors and structural proteins are involved.
- ✓ Unaffected children do not transmit disease to their offspring.

Examples.

- ✓ Marfan syndrome,
- ✓ Osteogenesis imperfecta,
- ✓ Achondroplasia,
- ✓ Ehlers-Danlos syndrom,
- ✓ Myotonic dystrophy.

Transmission Patterns of Single Gene Disorders Contd..

- **Autosomal Recessive disorders:**

✓ Occur when both copies of a gene are mutated and frequently involve enzyme proteins.

✓ Males and females are affected equally.

✓ Both parents are heterozygous carriers without symptoms because most homozygotes die before reaching reproductive age.

Examples.

- ✓ Sickle cell anemia,
- ✓ α & β thalasemia,
- ✓ Hereditory hemochromatosis,
- ✓ Gaucher diasease,
- ✓ Myeloperoxidase deficiency,
- ✓ Cystic fibrosis.

Transmission Patterns of Single Gene Disorders Contd..

- **X-linked disorders:**

✓ Disease occurs only in males.

✓ Heterozygous females are carriers without evidence of disease,

✓ Such females are usually protected because of random inactivation of one X chromosome.

Examples.

- ✓ Fragile X syndrome,
- ✓ Duchenne-Becker muscular dystrophy,
- ✓ Hemophilia A,
- ✓ Lesch-Nyhan syndrome.

Alteration in structure, function or quantity of non enzyme proteins.

- **Protein** data base shape determines **function.**

- Any slight change to a **protein's shape** may cause **protein** to become dysfunctional.

Contd…

- Small changes in the amino acid sequence of a **protein** can cause devastating genetic diseases such as Huntington's disease or sickle cell anemia.

- **Mutations** result in reduced **protein function** or no **protein function**.

Contd…

- **Leaky Mutation:** A mutation with reduced function.

- **Null Mutation**: A mutation that results in no protein function.

Why autosomal dominant disorders usually affect structural proteins & receptors rather than enzymes?

- Structural proteins & receptors are associated with dominant inheritance because they typically interact to form multimeric complexes.
- The presence of defective protein in patients with one mutant allele may be sufficient to render the entire complex nonfunctional.

e.g.

- Patients with osteogenesis imperfecta synthesize an abnormal collagen chain that blocks the assembly of trimeric collagen fibrils.

Contd…

- In contrast, enzymes are commonly associated with recessive inheritance because a 50% reduction in enzyme activity in patients with one mutant allele is typically corrected by increasing substrate concentration.

Contd…

- Complete(100%) reduction in enzyme activity in patients with two mutant alleles cannot be corrected and is associated with clinical evidence of disease.

Genetically determined adverse reactions to drugs.

- Some genetically determined enzyme deficiencies are unmasked only after exposure of the affected individual to certain drugs.

- E.g. Deficiency of enzyme Glucose-6 phosphate-dehydrogenase (G6PD).

Contd…

- Under normal conditions, deficiency does not result in disease but on administration of e.g. antimalarial drug primaquine, a severe hemolytic anemia results.

Pharmacogenetics.

- Study of how people respond differently to drug therapy based upon their genetic makeup or genes.

- In other words administring right drug in right dose.

Contd…

- It usually refers to how variation in one single gene influences the response to a single drug.

- It is hoped that advances in this field will lead to “personalised medicine” (patient tailored therapy).