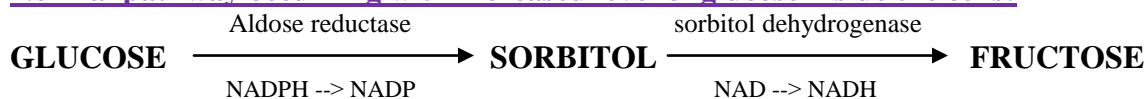




- The polyol pathway is also known as the sorbitol pathway. It is specific and not occurring in all types of cells.
- In glycolysis:
 - **A kinas enzyme (hexokinase):** is going to add phosphate to the 6th carbon position of glucose (addition of a negative charge) → this will result in trapping of glucose inside the cell.
 - **If level of glucose inside the cell is highly increased (hyperglycemic condition)** → it can be converted to sorbitol (especially in: lens – retina – Schwann cells of peripheral nerves – liver – kidney – RBCs – ovaries and spermatozoa).
- Normal pathway occurring with increased level of glucose inside the cells:



Note that NADH which is generated in this pathway can be used to produce energy (each NADH can produce 3 ATP molecules).

- These cells which were mentioned above are insulin-independent which mean that glucose can enter them without the presence of insulin. If these cells get flooded with glucose, polyol pathway will get activated and large amount of sorbitol will be produced. If the enzyme sorbitol dehydrogenase is abscent or low (retina, lens, kidney and nerve), sorbitol will accumulate resulting in an osmotic effect which will lead to water retention contributing to pathologic conditions seen in diabetes such as nephropathy, neuropathy and retinopathy.
- Excessive use of NADPH by aldose reductase decreases the generation of reduced glutathione (an important antioxidant) → this will cause oxidative stress.
- Activation of polyol pathway:
 - **Aldose reductase has a low affinity for glucose** (which means that it will not be activated unless the level of glucose is high).
 - **When cellular glucose level is high** → glycolysis will occur first followed by polyol pathway (if glucose levels are still high) → both of them will produce high level of NADH which will cause a negative feedback of the enzyme srobitol dehydrogenase.
 - **Aldose reductase can also act on galactose and convert it to galactitol** (which has a similar effect of sorbitol).
- Diabetic eye disease (the following diseases don't only happen in diabetic patients):
 - **Retinopathy:** damage to the blood vessels in the retina leading to spotted vision.
 - **Cataract:** the lens of the eye will be damaged resulting in blurred vision.
 - **Glaucoma:** increase in fluid pressure inside the eye which leads to optic nerve damage and loss of vision.
- Diabetic retinopathy:
 - It is a common cause of blindness in working age people.
 - **Pathogenesis:**
 - ✓ Polyol sorbitol pathway.
 - ✓ Oxidative stress.
 - ✓ Redox potential abnormality.
 - ✓ Non-enzymatic glycation process.
- Nitric oxide: it was known as endothelial derived relaxing factor.
 - **Function:** vasodilation.
 - **Important clinical significance:** in cardiovascular diseases – treating male impotence – protection of cardiac transplants from rejection – regulation of renal function – management of septic shock.
 - **Role of NO in the nervous system:**



- ✓ Acting as a neurotransmitter from a presynaptic to a postsynaptic neuron.
- ✓ NO is small, uncharged and fat-soluble thus it can diffuse to nearby neurons even if they are not connected by synapses.
- ✓ NO has a short half-life. Therefore, it will cause an effect which is restricted for a limited area in a limited time (it is self-limiting).
- ✓ NO-cGMP is involved in learning and memory through the maintenance of long term potentiation.
- ✓ It is an important non-adrenergic non-cholinergic neurotransmitter in the GIT → leading to relaxation of smooth muscles.

- **Vitamin-B complex and the nervous system:**

- **B1 (thiamine):** Na-transport across the neuron cell membrane.
- **B2 (riboflavin):** a component of FAD and FMN which are considered as coenzymes in the respiratory chain of neurons (providing energy to the neuron).
- **B3 (Niacin):** ↑ the response to neurotransmitters and hormones. In addition, it is a component of NAD and NADP which are considered as coenzymes for many dehydrogenases in carbohydrate and lipid metabolism.
- **B6 (pyridoxine), B7 (biotin), B9 (folic acid):** help in biosynthesis of neurotransmitters.
- **B12 (cyanocobalamin):** inhibiting myelin destruction.