Regulation of cholesterol synthesis

Cholesterol is an amphipathic lipid commonly found in our food. Even so, the body synthesizes 500 mg of cholesterol de novo every day. It has considerable biomedical significance. It forms the plasma membrane of all cells, the main component of **bile acids** and is a precursor of **steroid hormones** and **vitamin D**. However, an excessive amount of cholesterol in the blood is a factor that increases the risk of cardiovascular disease. The level of cholesterol in the blood is, on the one hand, determined by the amount of it taken in with food, and on the other hand, it is maintained by the application of cholesterol synthesis regulation mechanisms, especially by means of the activity of **HMG-CoA reductase** .

HMG-CoA reductase

HMG-CoA reductase is a key enzyme for cholesterol synthesis. It reduces HMG-CoA to mevalonate. It is active when dephosphorylated.

Quick regulation

- **Competitive inhibition**

  Inhibition using statins (lovastatin), which are used in practice to lower cholesterol levels.

- **Covalent modification (reversible phosphorylation)**

  Inhibition by phosphorylation catalyzed by AMP-dependent protein kinase. Protein kinase is active when the level of AMP is high in the cells. For example, glucagon and epinephrine increase cAMP in cells, which decrease the level of AMP and therefore decrease cholesterol synthesis. On the contrary, insulin and thyroxine increase the activity of HMG-CoA reductase, decrease the level of cAMP in the cell, thus increasing cholesterol synthesis

Slow regulation

- **Regulation of transcription**

  1. **Feedback inhibition by cholesterol**
  A sufficient amount of cholesterol in the cell suppresses the transcription of the gene for the formation of HMG-CoA reductase, which means that cholesterol synthesis is reduced. On the contrary, when there is little cholesterol in the cell, its synthesis increases.

  2. **Control of HMG-CoA reductase gene expression**
  The mechanism by which cholesterol controls the expression of the gene for the enzyme HMG-CoA reductase (and at least 20 other genes, including the gene for the LDL-receptor) is hidden in a DNA sequence called an SRE (sterol regulatory element).
  SREBP (sterol regulatory element binding protein) is an integral membrane protein on the membrane of the endoplasmic reticulum of cells. It binds and activates SCAP (SREBP cleavage-activating protein), which functions as a sterol (cholesterol) sensor.
  When there is enough cholesterol, SCAP remains inactive bound to cholesterol.

  3. **Proteolytic degradation of HMG-CoA reductase**
  Should cholesterol depletion occur, the SREBP-SCAP complex travels to the membrane of the Golgi apparatus , where S1P and S2P proteases cleave SREBP into a protein that binds to the SRE DNA sequence and activates HMG-CoA reductase transcription.

Links

Related Articles

- Cholesterol
- Transcription

References

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