

# Complex mechanisms in Gaucher disease unravelled

March 30 2017

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Gaucher disease is a genetic disorder of lipid metabolism. Sphingosine, a compound as enigmatic as the sphinx, plays a key role in this metabolic disorder. Scientists from the Bonn research center caesar have identified some of the complex molecular mechanisms of how the disease develops. These findings could contribute to the development of new therapies in the future.

There are very different manifestations of Gaucher disease: some patients suffer from serious neurological disorders and often die in childhood. Other patients are particularly affected by organ enlargement, especially the liver and spleen. The symptoms can be mitigated by medication. Today, it is known that a mutation in a particular gene, the so-called GBA1, is responsible for the disease. However, it is puzzling why one and the same mutation causes such different symptoms and clinical pictures.

## **GBA1 degrades lipid-fat compounds**

Scientists from the research group "Molecular Physiology", headed by Dagmar Wachten, have looked more closely at the metabolic processes. The gene sequence GBA1 is responsible for the production of the enzyme GBA1, which plays an important role in the degradation of complex lipid-sugar [compounds](#). Such lipid-sugar compounds, also referred to as glycosphingolipids, are building blocks of cell membranes. In the cell, old membrane building blocks are permanently removed and

replaced by new ones. This is achieved by the lysosomes, cell organelles, which fulfill the tasks of a waste recycling plant in human and animal cells. In the lysosomes, the enzyme GBA1 becomes active and degrades the glycosphingolipids into smaller fragments.

In patients suffering from Gaucher disease, the enzyme GBA1 does not function properly. As a result, the lysosomes swell and finally overflow like a garbage can: lipid-sugar compounds spill out of the lysosomes and swim around in the cell. Now a first [emergency plan](#) comes into force: The enzyme GBA2 takes over and splits the lipid-sugar compounds outside the lysosomes. In this degradation process, inter alia, sphingosine is produced. Sphingosine was discovered over a hundred years ago by a German researcher, who named the enigmatic substance in reference to an Egyptian sphinx. Unfortunately, sphingosine is toxic to the [cells](#). To prevent the poisoning of the cell, a second emergency plan regulates the activity of the enzyme GBA2.

## **Sphingosine inhibits GBA2**

To unravel this regulatory mechanism of the cell and to visualize the activity of the enzyme GBA2, the scientists have applied a trick. The sugar-lipid compound to be degraded was replaced by an analogous compound, whose degradation produces a fluorescent product. Measuring this fluorescence thus makes the activity of the enzyme visible. In this way, the researchers could show that the activity of the enzyme GBA2 is inhibited by sphingosine. Experiments in living organisms and in the test tube always produced the same results: The higher the sphingosine concentration in the cell, the less active is GBA2. The researchers also discovered the mechanism behind this. Sphingosine binds to GBA2 and thus reduces the activity of the enzyme. This effect is reversible - as soon as the sphingosine concentration decreases, the [enzyme](#) GBA2 returns to its old form.

The regulatory mechanisms decrypted by the caesar scientists could in the future help to develop new therapies for Gaucher disease patients. However, there are still questions open: Why do the same genetic defects and biochemical findings cause such different clinical pictures? Is there a link between the activity of GBA2 and the neurological disorders that may be associated with Gaucher disease? Is there a way to intervene in the degradation of lipid-sugar compounds in the cell in a way that toxic degradation products, such as sphingosine, do no harm?

**More information:** Sophie Schonauer et al. Identification of a feedback loop involving beta-glucosidase 2 and its product sphingosine sheds light on the molecular mechanisms in Gaucher disease, *Journal of Biological Chemistry* (2017). [DOI: 10.1074/jbc.M116.762831](https://doi.org/10.1074/jbc.M116.762831)

Provided by Max Planck Society

Citation: Complex mechanisms in Gaucher disease unravelled (2017, March 30) retrieved 24 April 2024 from <https://medicalxpress.com/news/2017-03-complex-mechanisms-gaucher-disease-unravelled.html>

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