Prof. Dr. med. Werner Reutter

Galactose Rediscovered

A Food With Healing Powers

Our consumer society is taking its toll. People are increasingly becoming diabetic and obese, suffering from high blood pressure and sometimes gout. These symptoms (elevated blood sugar levels, elevated blood pressure, high blood lipid and uric acid levels) are grouped together under the term "metabolic syndrome" This usually progresses to cardiovascular disease with complications such as vascular occlusion in the legs or heart attack. Diabetes, obesity, and gout rarely occurred in times of hunger like those after the two wars in Europe. In the USA today, over 25 % of the population suffer from these lifestyle diseases, and the number is growing. Europe is on target to reach this percentage as well. Children are set on this track with the daily consumption of cola, French fries, and hamburgers.

Alzheimer's disease, which is also on the increase, has a number of things in common with type 2 diabetes mellitus. Diabetics suffer from Alzheimer's disease more often than nondiabetics, and both disorders have a common cause. A single molecule is resposnitlble for the pathophysiological relationship between these diseases, whose symptoms are so different: the insulin receptor. Its importance is the topic of this article.

Pathobiological Background

Insulin

Insulin is the most important hormone in the regulation of the metabolism of carbohydrates and fats in the animal organism. It has long been known that it is produced in the ß-cells of the pancreas; more recently, it has been found that the brain is also able to synthesize and secrete insulin.

This peptide hormone has three important functions:

1. Supplying vital organs with glucose. This primarily includes the brain and red blood cells, which use exclusively glucose as their only nutrient. They cannot use amino acids or fatty acids, unlike other major organs like the fatty tissues and muscles.

2. Maintenance of a normal concentration of blood glucose. An excess of glucose in the blood causes insulin to promote flow into the musculature and fatty tissues. Excess glucose leads to its conversion and storage as glycogen, which is also promoted by insulin. Insulin uses both of these pathways to maintain a "normal" blood glucose concentration.

3. Insulin is able to induce the cell nucleus to synthesize proteins, growth factors, and enzymes that are used in energy generation (glycolysis). This process is known as enzyme induction.

An inadequate supply of glucose causes cells to enter into a stavation state and to begin losing all biological function. These effects impact the messenger substances of the central nervous system (CNS). Examples of such messenger substances include acetylcholine, which is responsible for the nomral formation of memoris; serotonin, which a ffects the cardiovascular and gastrointestinal systems, as well as our sense of well-being ("happiness hormone"); γ-aminobutyric acid (GABA), which inhibits neuronal stimulaiton; and glutamate, which ensures rapid signal conduction. Important areas of the brain for controlling memory include the hippocampus (in the limibic system) and the hypothalamus (in the diencephalon).

Insulin receptors and insulin resistence

Insulin can only carry out its biological function within a cell when it is recognized by a specific antenna on the surface of that cell, the insulin receptor. This receptor is necessary because, as a polypeptide, insulin is not able to pass through the cell membrane; it needs a mediator on the cell's surface. When insulin is recognized by the receptor, it sends a signal to the interior of the cell so that glucose-transporting molecules (called GLUT4) are brought from the cytosol to the cell membrane. These then carry the glucose into the cell.

This process is highly specific and also very susceptible to disruption. Small changes to the receptor molecule lead to a reduction in its ability to function so that the insulin can no longer transmit its message to the interior of the cell as effectively. Damage to the insulin receptors of muscle and fatty tissue cells leads to a rise in the blood glucose concentration if the supply of glucose from food is not reduced.

In the case of type 2 diabetes mellitus, the insulin receptors of the ß-cells in the pancreas are damaged. The cause of the damage can vary: elevated blood sugar levels, stress-induced changes to the hormone metabolism (cortisol, adrenalin), lack of physical activity.

Biochemically, the damage to the receptor is caused by the attachment of a product that results from elevated glucose: the amino sugar N-acetylglucosamine, which gets enzymatically linked to the amino acid serine and deactivates the receptor, as discovered by researchers working with G. Hart

Prof. em.
Dr. Med.
Werner Reutter

Research in physics and medicine, Professor of Biochemistry from 1979 until 2005, now Emeritus Professor and Visiting Scientist and director of a research team at the Institute for Biochemistry and Molecular Biology at the Medical School of the Free University of Berlin (known since 2003 as the Charité University Medicine Berlin Campus Benjamin Franklin). During his professorship, he was chairman of the Collaborative Research Centre 366 "Cellular Signal Recognition and Conversion", Managing Director of the Institute for Biochemistry and Molecular Biology, Vice President of Medicine and Research of the Free University of Berlin, Technical Advisor for the German Research Foundaiton (DFG) in the area of biochemistry, President of the German Association for the Study of the Liver (GASL), and Scientific Director of the Dahlem Conferences of the Free University of Berlin. Recipient of the Gerhard-Domagk Prize for cancer research and the Sasse prize for the advancement of immunotherapy.

Contact:
Institut für Biochemie
und Molekularbiologie
Charité Campus Benjamin Franklin
Arnimallee 22, D-14195 Berlin-Dahlem
Tel.:030/83871350
werner.reutter@charite.de

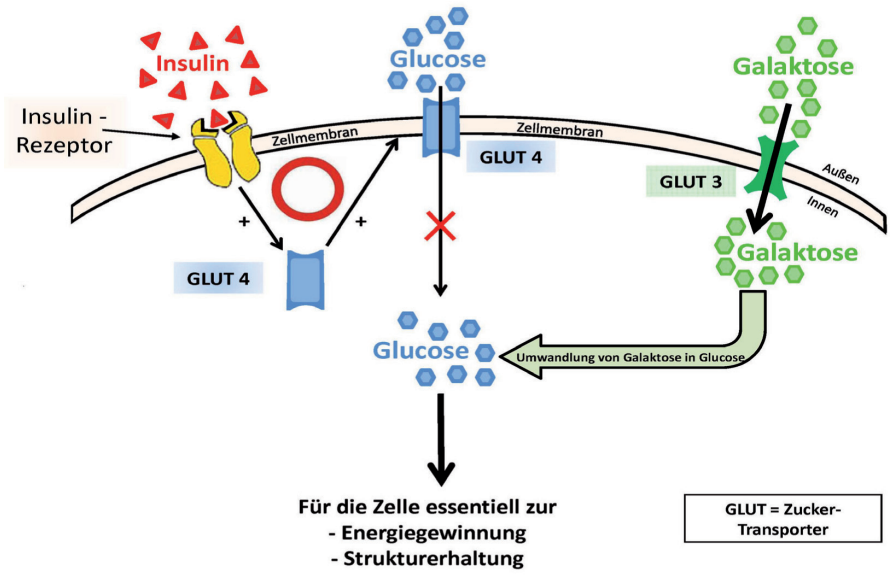

Fig. 1: Comparison of glucose and galactose transport into a cell by means of GLUT4 and GLUT3, respectively.

(Baltimore, MD) and J. Hanover (NIH, Washington DC).

Type 2 diabetes mellitus can be experimentally induced in rats by the injection of a toxin (STZ) into the abdomen. This toxin switches off the function of the insulin receptors in pancreatic ß-cells. The isolated injection of this same toxin into the hippocampus can cause symptoms similar to Alzheimer's disease in rats by switching off the insulin receptors in this region of the brain. This drastically reduces the supply of glucose in the hippocampus and significantly reduces the memory capacity of the affected rats. This highlights a pathobiological commonality between diabetics and Alzheimer's patients: damage to the insulin receptors, in the pancrease for diabetes, in the brain for Alzheimer's disease. For this reason, Alzheimer's disease is also classified as type 3 diabetes mellitus (S. de la Monte, Providence, RI).

Metabolic circumvention of insulin receptor defects

There are various transportation systems for carrying monosaccharides into cells. The specific, insulin-dependent transport of glucose by the glucose transporter GLUT4 is described above. Of the fourteen known glucose transporters, GLUT3 offers a way to circumvent the insulin-dependent, and thus problematic, GLUT4. Neuron-specific GLUT3 preferentially transports galactose.

It is critical the GLUT3 works without help from insulin. It only depends on a concentration gradient, which must form for GLUT3 activation to occur.

The ingestion of relatively large amounts of galactose is thus a prerequisite for a successful recovery from a diseased condition. [1]

Figure 1 compares the two transport systems. If galactose enters a cell by means of GLUT3, it is rapidly and quantitatively metabolized into glucose (Leloir pathway). This remedies the glucose deficiency in the cell.

Galactose is a nutrient obtained from whey, which contains lactose (lactose = galactose + glucose). Despite its galactose content, lactose, which is much less expensive, cannot be used in place of galactose because it must first be broken down in the small intestine to release galactose. This is problematic for two reasons:

1. Although every suckling baby has the enzyme required (suckling lactase), adult lactase is not present in nearly 10 % of Europeans and 25 % of all people worldwide. (who then suffer from lactose intolerance). For these individuals, consuming lactose leads to painful gastrointestinal cramping, bloating, and diarrhea.
2. In addition, lactase in the adult small intestine (as opposed to infant lactase) is a minimally active enzyme that cannot release enough galactose from lactose . The amount of galactose expected from this process would not achieve the required galactose gradient at the cell membrane.

Galactose is able to successfully circumvent insulin resistance by a metabolic pathway; however, it is no replacement for physical activity, which is important, necessary, and healthful, and must be strongly recommended to patients. Increased activity often makes it possible to normalize an elevated insulin concentration in the blood and to increase the recognition abilities of the insulin receptor.

Why "rediscovered"?

As early as the 1930s, galactose was successfully used at the Charité Hospital Berlin for the treatment of patients with severe type 2 diabetes mellitus. Surprisingly, ketonemia (the fruity smell of the breath) disappeared, and the amount of insulin required was reduced. Resident Hans Kosterlitz was unfortunately not able to continue his investigations at the time, because he was forced to leave Germany (at the University of Aberdeen, he went on to be the first to describe endorphins). The blood sugar levels of the patients he treated with galactose did not rise, which is an important prerequisite for use in diabetics. This was later confirmed by other research groups.

Other diseases involving defective insulin receptors

The central role played by the control function of the insulin receptor in ensuring a sufficient supply of glucose to the cell is particularly evident in the central nervous system. Because glucose is the only nutrient involved, it is no wonder that disorders such as Parkinson's disease, restless legs syndrome, ADHS, and burnout syndrome, to name a few, react favorably to the administration of galactose.

Outlook

If galactose is effective it means that the functionality of the insulin receptor is compromised

[1] Dosage: Galactose is a powder and easily dissolves in tea, water, or other liquids. The recommended dosage is one teaspoon of galactose taken two or three times a day.

Because the insulin receptor is expressed and active in nearly all human cells, it is not unthinkable that the administration of galactose may be effective against diseases beyond those mentioned above. One example may be the use of galactose in cases of osteoporosis, because bone cells can only maintain their structure when supplied with enough glucose. However, little is currently known about the age-dependent activity of the insulin receptors in these cells. The same could be said of muscle cells in various types of myopathy, such as Duchenne muscular dystrophy. Surprisingly, it has recently been found that in patients with severe cardiac insufficiency, the administration of galactose produces a signficant improvement in heart function. Because the insulin receptor also has an important function in the heart muscle, this raises the biochemical question of whether this disorder also involves damage to the insulin receptor, which leads to relief when galactose is given.

The therapeutically effective properties of galactose described here are based on findings from basic research that is still in its infancy.

Further biochemical and molecular biological investigations are urgently indicated. These could build upon early studies carried out on yeasts and bacteria in the 1950s and early 1960s (Jacob, Monod, Wyaman). These showed that relatively high concentrations of galactose could induce cell nuclei to produce more proteins (enzyme induction). The use of a similar research approach on animal cells could help to explain the mechanisms by which galactose works, not only by way of the glucose pathway, but also in processes controlled directly by the cell nucleus.

References

Plum L, Schubert M, Brünning JC (2005): The role of insulin receptor signaling in the brain. Trends Endocrinol Metab 16:59-60

Liu F, Iqbal K, Grundke-Iqbal I, Hart GW, Gong CX (2004) O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. Proc Natl Acad Sci USA 101:10804-10809

Roser M, Josic D, Kontou M, Maurer P, Reutter W (2009): Metabolism of galactose in the brain and liver of rats and ist conversion into glutamate and other amino acids. J Neural Transm 116:131-9

Meyer G, Badenhoop K (2003): Glukokortikoidinduzierte Insulinresistenz und Diabetes mellitus. Med Klinik 98:266-70

Kosterlitz H, and Wedler HW: Untersuchungen über die Verwertung der Galaktose

in physiologischen und pathologischen Zuständen.

Die Verwertung der Galaktose beim Diabetes mellitus.

Die Galaktose als Ersatzkohlehydrat. Z Ges Exp Med 87:397-404

Hoyer S (2004) Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. Eur J Pharmacol 490:115-25

de la Monte S, Wands JR (2008) Alzheimer's Disease Is Type 3 Diabetes-Evidence Reviewed. J Diabetes Sci Technol 2:1101-13