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Severe congenital disorder successfully treated in a mouse model for the first time

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Using a mouse model, Heidelberg University Hospital researchers have for the first time successfully treated a severe congenital disorder in which sugar metabolism is disturbed. The team headed by Prof. Christian Korner, group leader at the Center for Child and Adolescent Medicine, demonstrated that if female mice are given mannose with their drinking water prior to mating and during pregnancy, their offspring will develop normally even if they carry the genetic mutation for the congenital disorder. The team's outstanding work will contribute to better understanding of the molecular processes of this metabolic disease, along with the key stages in embryonic development, and may offer a therapeutic approach for the first time.

The Heidelberg-based researchers also collaborated with colleagues working with Prof. Hermann-Josef Gröne of the German Cancer Research Center (DKFZ)'s Division of Cellular and Molecular Pathology in Heidelberg. Their results have now been published online in the internationally respected journal *Nature Medicine* in advance of their publication in the print edition.

Rare disease: Approx. 1,000 children affected

So far 1,000 children worldwide are affected by congenital disorders of glycosylation (CDG), which are classified as rare diseases. Affecting around 800 children, type CDG-Ia is most frequent. The number of unreported cases is high, however. Children with CDG are severely

physically and mentally disabled, with approx. 20 percent dying before the age of two. To date, no therapy has been available to treat the disorder.

CDG-Ia is caused by mutations in the genetic information for the enzyme Phosphomannomutase 2 which is involved in important glycosylation processes: Mannose-1-phosphate is not produced in sufficient quantities. As a result, glycosylation malfunctions, meaning that sugar chains that normally aid in form, stability and function of the glycoproteins are not completely attached to the body's proteins or in some cases, are not attached at all. The lack of oligosaccharide chains leads to impairment of neurological, growth and organ development. The disorder only manifests if the baby inherits a mutated gene from both the mother and the father. The parents, who each carry one mutated and one "healthy" copy of the gene, do not exhibit any symptoms.

Mice take up mannose in drinking water

The mouse model developed by Prof. Körner and his team is characterized by mutations in the Phosphomannomutase 2 gene and demonstrates reduced enzyme activity, comparable to CDG-Ia in man. In their current study, the scientists exploited the ability of mannose to cross the placental barrier. This means that if the pregnant mouse takes up mannose, it also reaches the embryos in the uterus.

"One week prior to mating, we began giving the female mice mannose with their drinking water," explained biochemist Prof. Körner. The additional mannose supply up to birth increased the mannose levels in the embryos' blood. "The mice were born without defects and also after they were born, developed without any symptoms of the disorder, even if they no longer took up any mannose," Körner added. The successful studies performed by the Heidelberg University Hospital researchers clearly show the key role played by the supply of proteins with sugar

chains during embryonic development.

New therapeutic approach

"Clinical studies in the U.S. and Germany have already been performed in which children with CDG-Ia were given mannose after they were born, either orally or by intravenous infusion. Unfortunately, these attempts have not been successful," explained Dr. Christian Thiel, head of the laboratory. "This means that the critical point at which it is possible to influence development must be during development in the uterus." For women with a risk of CDG-Ia, administering mannose during pregnancy may serve as a new therapeutic approach.

More information: Successful prenatal mannose treatment for congenital disorder of glycosylation-Ia in mice. Anette Schneider, Christian Thiel, Jan Rindermann, Charles DeRossi, Diana Popovici, Georg F Hoffmann, Hermann-Josef Gröne & Christian Körner. *Nature Medicine* doi:10.1038/nm.2548

Provided by University Hospital Heidelberg