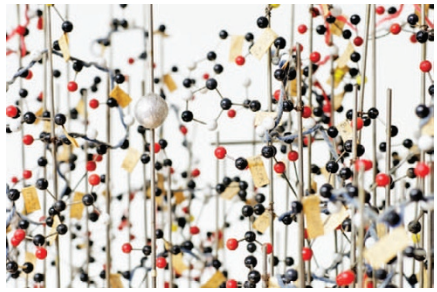
Targeting fat storage to treat type II diabetes

Type II diabetes affects approximately 310 million individuals worldwide, and its prevalence is rapidly increasing. The disease is normally preceded by insulin resistance that results from obesity. The excess storage of fat in extra-adipose tissues, especially cardiac and skeletal muscles, impairs the ability of cells to respond sufficiently to insulin, leading to elevated glucose levels in the blood. Few treatments for type II diabetes directly target this fat accumulation. Now, an international team of collaborators led by Ulf Erikkson (Karolinska Institute, Stockholm, Sweden), together with researchers at the University of Melbourne (Heidelberg, Australia) and at the drug company CSL, Ltd. (Parkville, Australia), have found that blocking the signaling of a protein called VEGF-B prevents fat from accumulating in muscles and in the heart so that the cells in these tissues are once again able to respond to insulin.

The researchers reported the results of four different studies of VEGF-B in *Nature* (published online 26 September 2012; doi:10.1038/nature11464). Two studies examined the effects of genetically deleting VEGF-B on diabetes development. Mice that genetically lacked the ability to produce VEGF-B were crossed with a strain of mice genetically prone to developing diabetes. The offspring produced from these crosses had normal blood glucose levels and decreased accumulation of fat in their muscles and heart. When VEGF-B was genetically deleted in mice that were fed a high-fat diet, the mice were similarly protected from developing diabetes despite gaining more weight. These findings suggest that VEGF-B is necessary in the development of type II diabetes.

In another study, mice of the same diabetes-prone strain were treated with an antibody against VEGF-B for 10 weeks, either preventatively (given to pre-diabetic mice) or therapeutically (given to diabetic mice). Treatment of pre-diabetic mice with the drug prevented the development of insulin resistance as well as storage of lipids in muscle and heart tissues. Treatment of the diabetic mice was also effective; the drug halted the progression of the disease. A final study applied the drug treatment to a group of rats fed a high-fat diet for 8 weeks and given the drug in parallel. The treatment restored insulin sensitivity, increased muscle glucose usage and reversed diabetes pathology in the rats.



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Said coauthor Ake Sjoholm in a press release, "The results we present in this study represent a major breakthrough and an entirely new principle for the prevention and treatment of type II diabetes."

Kara Rosania

DANGERS OF BPA EXPOSURE CONFIRMED IN RHESUS MACAQUES

Bisphenol A (BPA) is a synthetic chemical with endocrine-disrupting properties that is present in many consumer items: the linings of aluminum cans, heat-activated or pressure-printed cash register receipts, dental sealants and polycarbonate plastic products such as food and drink containers. Because of its prevalence, many people are exposed to BPA on a recurring basis. Data from the US Centers for Disease Control and Prevention suggest that BPA is present in the bodies of more than 90% of American adults.

Concerns regarding the risks of this widespread exposure have grown during the past 15 years, as hundreds of studies have reported adverse effects of low-dose exposure to BPA in animal models. In rodents, fetal and neonatal exposure has been shown to affect reproductive development in both males and females. But the relevance of results from rodent studies to human health has been questioned, in part because metabolism of BPA differs between rodents and humans, even though the pharmacokinetics of BPA within the body were recently reported to be quite similar in rodents, nonhuman primates and humans. To address these concerns, researchers led by Patricia A. Hunt (Washington State University, Pullman) evaluated the effects of BPA in animals more closely related to humans: rhesus macaques. The results provide evidence that exposure to BPA can alter chromosomes and affect reproductive viability in primates.

Hunt studied BPA exposure in pregnant macaques and their unborn female offspring and found that it caused damage during two stages of oogenesis. First, during early meiosis, Hunt's team observed disturbances in prophase events that affect chromosome segregation and could cause eggs to divide improperly, potentially resulting in birth defects (*Proc. Natl. Acad. Sci. USA* published online 24 September 2012; doi:10.1073/pnas.1207854109). Second, during follicle formation later in oogenesis, the group noted defects in oocyte packaging, which could limit the number of viable eggs in female offspring, impairing their fertility.

The results indicate that BPA exposure can affect multiple generations simultaneously: a pregnant female, her fetus and that fetus' future offspring, if the fetus is female. "It's a three-for-one hit," Hunt said (*USA Today*, 26 September 2012; http://usatoday30.usatoday.com/news/nation/story/2012/09/26/bpa-damages-chromosomes-in-monkeys/57838050/1). The implication is that the effects of BPA exposure may not be fully manifested for one generation, which could complicate efforts to establish direct links between exposure and adverse outcomes.

Hunt's findings in rhesus macaques confirm results of earlier studies in rodents and suggest that fetal exposure to BPA may adversely affect reproductive potential in humans.

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