Targeting drug delivery

To help increase blood flow through vessels that are narrowed or partially blocked, surgeons insert tiny metal mesh tubes called stents. Once inserted, stents expand inside of blood vessels. Stents are often coated with antiproliferative drugs, such as paclitaxel, to reduce the chance of blood vessel blockages related to stent-induced injury. Though stents have significantly improved therapeutic outcomes, the drug eluted by a stent cannot be changed and drug doses cannot be modified or replenished. In an effort to address these challenges, a team of researchers tested whether they could deliver drugs to rats' injured blood vessels by using a uniform magnetic field to direct drug-loaded magnetic nanoparticles to stents in these blood vessels.

Robert Levy of The Children's Hospital of Philadelphia (PA) and his colleagues injured the left carotid arteries of anesthetized male Sprague-Dawley rats (*Proc. Natl. Acad. Sci. USA* published online 19 April 2010; doi:10.1073/pnas.0909506107). They then placed a stent into the left carotid artery

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of each rat and used ligatures to isolate the region of the artery encompassing the stent. One group of the animals was then exposed to a uniform magnetic field. Next, the research team delivered paclitaxel-loaded biodegradable magnetic nanoparticles to the isolated arterial segment of each rat for 30 seconds and then released the ligatures. The animals in the magnetic field treatment group were then exposed to the field for an additional 5 minutes.

Analyses revealed that 2 and 24 hours after stent insertion, there were substantially more magnetic nanoparticles in the stent and the surrounding arterial tissue in the rats that had been exposed to the magnetic field than in control rats that had not been exposed. The rats in the magnetic field exposure group that had received magnetic nanoparticles containing a 7.5-μg dose of paclitaxel showed significantly inhibited in-stent restenosis 14 days after the magnetic treatment. The nonmagnetic injection of drug-loaded magnetic nanoparticles with the same dose of paclitaxel did not significantly inhibit growth of new tissue.

These results show that a magnetic field targeting approach, similar to the one described by Levy and his team, could potentially be used to help reduce the risk of in-stent restenosis in humans. Levy and his colleagues suggest that by combining efficient targeting techniques with the sustained drug release properties of magnetic nanoparticles, researchers could develop a safer and more efficacious alternative for treating diseased or injured blood vessels.

Kirsten Dorans

KNOCKING OUT COMPULSIVE BEHAVIOR

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by obsessive thoughts, compulsive repetitive actions and, often, anxiety and depression. Its underlying causes and pathology remain largely unknown, although a genetic component has been suggested. Now, scientists have identified a gene whose absence causes OCD-like behavior in mice. The gene encodes Slitrk5, a neuron-specific transmembrane protein that is widely expressed throughout the central nervous system.

Shahin Rafii and Francis S.Y. Lee (Weill Cornell Medical College, New York, NY) directed the studies, which used genetically engineered mice lacking *Slitrk5*. From 3 months of age, these knockout mice began grooming themselves excessively, causing hair loss and skin lesions (*Nat. Med.* published online 25 April 2010; doi:10.1038/nm.2125). They also showed increased anxiety-like behaviors in various types of behavioral testing (elevated-plus maze, open-field test and marble-burying test). Compulsive behavior and anxiety are core symptoms of OCD in humans, leading the researchers to evaluate whether there were other similarities between people with OCD and the *Slitrk5*-knockout mice. The scientists treated the knockout mice with a selective serotonin reuptake inhibitor (SSRI), a common treatment for people with OCD. Administration of the SSRI fluoxetine prevented the compulsive behavior in *Slitrk5*-knockout mice.

Next, the research group examined brain activity in the knockout mice and found excessive neuronal activity in the orbitofrontal cortex. Notably, people with OCD show a similar increase in activity in this area of the brain, a characteristic that has not been recapitulated in existing mouse models of OCD. The scientists also found structural abnormalities in the striatum of the brain, a region associated with reward and decision-making, in the knockout mice. Neurons in the striatum were less complex in knockout mice than in wild-type mice.

Overall, these results suggest that *Slitrk5* has a role in the development of OCD and OCD-like behaviors. *Slitrk5*-knockout mice could be useful in future studies investigating the pathogenesis of OCD. In addition, these mice may serve as a model of OCD for the development and assessment of potential therapies.

Rafii noted that few psychiatric disorders can be linked to a single gene and that it will be important to evaluate whether people with OCD have any alterations in *SLITRK5*. Furthermore, Lee warned, "We can't draw direct parallels between mice and humans, because OCD behavior in mice shows up as excessive self-grooming, and in humans there is a broad spectrum of behaviors, from hand-washing to other compulsive actions as well as obsessive thoughts."

Monica Harrington