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A Magnetic Remote Control That Can Rewind a Worm's Wriggle

Researchers use heated magnetic nanoparticles to manipulate nerve cells and control simple behavior in nematodes

By Ferris Jabr

The power to control living things and objects from a distance is a popular supernatural talent in science fiction and fantasy: Witches fling spells at foes and X-Men send chairs and tables flying with telekinesis, for example. But when it comes to remotely controlling biological organisms, science has a few tricks up its sleeve, too—although there's nothing metaphysical about them. Manipulating biological processes with minimal interference, from the cellular level to the behavior of whole organisms, is a burgeoning scientific effort to better understand how living things work and to develop more effective treatments for a range of medical disorders.

Most recently, researchers essentially created a magnetic remote control that alters cell function and changes the behavior of a tiny worm. A team of biophysicists from the State University of New York (S.U.N.Y.) at Buffalo used magnetic nanoparticles to control heat-activated protein gates called ion channels embedded in the membranes of nerve cells, allowing the researchers to stimulate a simple reflex in nematode worms at will. This is the first time scientists have combined heat and nanomagnetic particles to control cellular function, and the new technique, published online June 27 in *Nature Nanotechnology*, offers certain advantages over earlier and alternative methods of ion-channel manipulation.

"The idea is to initiate specific biochemical processes in cells by flipping a magnetic switch," says Jon Dobson, a biomedical engineer who has been manipulating cellular function with magnetic particles for more than 10 years at Keele University in Staffordshire, England. "The nice thing about magnets is you don't actually have to touch the cell to turn it on or off—it's remote control."

If you want to control the processes inside living cells, you have to confront the gatekeepers—the molecular pumps, pores and channels that regulate the transport of particles in and out of a cell. Nerve cells rely on ion channels and pumps to orchestrate the continual ebb and flow of charged particles across the cell membrane, which enables the electrical signaling that nerves use to communicate. Before you can fiddle with an ion channel, you need to figure out what opens it—you have to find the right key.

Different ion channels respond to different kinds of stimulation. Some jellyfish, algae and bacteria produce light-activated ion pumps and channels. Other ion channels respond to mechanical force. Still others only open when the right molecule binds to them. In the new study, scientists focused on temperature-sensitive ion channels that open when they become hot enough. The researchers bound nanoparticles to cell membranes and used magnetic fields to heat the nanoparticles, which in turn switched open the heat-activated ion channels embedded in the cell membranes.

"What's unique about this study is that it uses heat, so you don't have to rely on such a strong magnetic field," Dobson says. He further explains that most previous work primarily used tiny magnets to open ion channels by pushing or pulling them in the right manner. "To mechanically twist or pull a particle requires a very strong magnetic field. To heat them, the strength of the field can be quite a bit lower," he says. Magnetic manipulation also offers advantages over optogenetics, a relatively new technique that precisely stimulates or silences neurons using beams of light. Whereas visible light cannot penetrate biological tissues deeply and must be applied to highly specific groups of cells through invasive procedures, magnetic fields are noninvasive and easily penetrate entire organisms.

The S.U.N.Y. Buffalo team decided to test whether they could control a simple reflex in the one-millimeter-long nematode worm *Caenorhabditis elegans* by manipulating the heat-activated ion channels in its sensory neurons. Whenever *C. elegans* detects noxious heat it instinctively recoils and crawls backward to avoid potential harm—a behavior that relies on temperature-sensitive ion channels. The team's goal was to trigger this reflex with a magnetic remote control.

Before injecting nematodes with magnetic nanoparticles, the scientists first coated the manganese–iron nanoparticles with polyethylene glycol, a molecule that targeted the particles to the mucus layer of the amphid region (an opening near the nematode's mouth that hosts the nerve cells involved in the heat avoidance reflex). They then applied a radio frequency electromagnetic field that heated the nanoparticles by forcing them to continuously switch their own polarities, releasing heat in the process. The rise in temperature opened the ion channels in the amphid region nerve cells, allowing an influx of calcium ions that triggered the heat-avoidance reflex.

Within five seconds of applying the magnetic field, 34 out of the 40 worms in the study stopped in place, and 27 of those worms moved backward, as though retreating from a dangerous heat source. The nematodes without magnetic nanoparticles continued to wriggle forward, completely unaffected by the magnetic field.

Forcing worms into rewind with a remote control might seem like the crowning achievement of the new study. The researchers, however, first tested their technique on cell cultures before they advanced to whole organisms—an approach that demonstrates greater experimental sophistication. "It's well known that you can inject magnetic nanoparticles and heat them up, so for me the nematode study is not as elegant as the earlier tests," Dobson says. "The really interesting thing they did was to genetically engineer cells to express heat-sensitive ion channels—that's a real innovation, in the first part of the paper."

Before toying with worms, the S.U.N.Y. Buffalo team tried out their technique on cultures of human embryonic kidney cells and neurons from a rat hippocampus, a part of the brain integral to memory. Whereas in the nematode experiment the researchers targeted nanoparticles to temperature-sensitive ion channels that naturally exist in the membranes of the worms' nerve cells, the scientists inserted the gene for a heat-activated ion channel called TRPV1 into the human and rat cells. But engineering cells to express TRPV1 was just one step in the complex process. The researchers also needed a way to bind the nanoparticles to the cell membrane so they could influence TRPV1 activity. To accomplish this, the scientists turned the cell membranes and nanoparticles into a kind of complex lock and key.

Instead of coating the nanoparticles with polyethylene glycol, the researchers covered them with a bacterial protein called streptavidin. They also engineered the cells to express certain peptide molecules in their membranes, which acted like locks for streptavidin, ensuring the nanoparticles would bind to the cell membrane. The scientists further coated the nanoparticles with a fluorescent molecule called DyLight549, which functions as a molecular thermometer, glowing with different intensities at different temperatures.

After outfitting the nanoparticles with their molecular assistants and engineering the cell membranes to receive the nanoparticles, the team applied a solution of nanoparticles to the cell cultures and switched on a magnetic field. Almost immediately, the fluorescence emitted by the cells changed: Right along the cell membranes, the intensity of the fluorescence decreased, which indicated (counterintuitively) that the temperature was rising in that locus and nowhere else in the cell. In other words, the researchers achieved incredibly localized heating of cell membranes without affecting the rest of the cell.

The heat was enough to activate TRPV1, opening the channels to a flood of calcium ions and triggering the kind of action potentials (electrical signaling) that guides nerve cell function.

"In principle what we are doing is letting calcium influx into a cell remotely," says Arnd Pralle, an assistant professor of physics at S.U.N.Y. Buffalo and a co-author of the *Nature Nanotechnology* study. "If you think about biology, there are a lot of cell events that are triggered by calcium influx and subsequently make a cell secrete something or make a muscle twitch." Pralle explains that remote control of ion channels could eventually lead to unprecedented precision in manipulating biological processes—with significant clinical and therapeutic potential.

Using heat to destroy tumors is one possible application, Pralle suggests. Treating paralysis or encouraging dysfunctional organs to secrete vital compounds are also possibilities. "I think certainly there's a lot of potential in this whole area," Dobson says. "The particles are relatively well tolerated in the body and we can basically control when things are turned on or off. But there's a lot more clever work that needs to be done before it gets into clinic."

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