NEUROSCIENCE

Neurons pick up the heat

Non-invasive neuronal stimulation deep within the brain is possible by tapping into an alternating magnetic field using magnetic nanoparticles.

Areas deep in the brain are difficult to stimulate with optogenetic tools, as light does not penetrate deeply into the tissue. Alternatively, these areas can be addressed with implanted electrodes, but such an invasive approach can result in tissue damage. Polina Anikeeva and her colleagues at the Massachusetts Institute of Technology recently established a minimally invasive method to stimulate deep brain structures using the heat generated by magnetic nanoparticles in an alternating magnetic field—which results in the activation of heat-sensitive TRPV1 channels (Chen *et al.*, 2015).

Anikeeva and her team were excited about using magnetic fields for deep brain stimulation because "they essentially penetrate through the tissue really deep, so the human body is transparent to them and doesn't interact." The challenge was to convert the energy of the magnetic field into a stimulus that addresses neurons. Magnetic nanomaterials such as the iron oxide magnetite are ideal, as they generate heat when placed in an alternating magnetic field. Heat dissipation from these particles is fast and efficient and, within a few seconds, results in a transient increase of the local temperature, which can then be read by TRPV channels that are expressed either from a transgene or endogenously.

Establishing this technique *in vivo* required tweaking the nanoparticles as well as the magnetic field because the amounts of generated and dissipated heat depend on both the composition of the particles and the conditions of the magnetic field, according to Anikeeva. "We spent a couple of years trying to synthesize magnetic nanoparticles with different compositions and sizes and at the same time developing custom coils to be able to tune the conditions of the alternating magnetic field," she says. For instance, the magnetic coils that she and her colleagues now use are shaped like donuts with a bite taken out. This shape focuses the magnetic field to the gap in the ring, where the mouse head can then be placed for magnetic stimulation.

To demonstrate their method *in vivo*, Anikeeva and her colleagues chose an area in the mouse brain that essentially does not express TRPV channels. This allowed them to express TRPV1 in a subset of neurons while the remaining cells served as controls. In other brain regions, TRPV channels may be endogenously expressed. "It will depend on the application whether this is a plus or a minus," says Anikeeva.

One approach to increasing the specificity of neuronal activation may be to target magnetic nanoparticles to particular cells. Francisco Bezanilla and his colleagues from the University of Chicago recently reported the targeting of gold nanoparticles to neurons in culture expressing voltage-gated sodium channels (Carvalho-de-Souza *et al.*, 2015). In this case, they used light to heat up the nanoparticles. The localized heat at the neuronal membranes was sufficiently high to modulate membrane capacitance and to directly trigger neural activity without the need for TRPV channel expression.

Anikeeva does not think that membrane capacitance is affected when using magnetic nanoparticles. "In the manipulations that we have done right now, it does not appear to be a viable mechanism; but if we were to develop particles that are more efficient and we can stimulate faster, then I think modulating membrane capacitance will become an issue," she says. Nevertheless, she thinks that targeting specific cells would be desirable, even though "specific targeting *in vivo* is very challenging because of the formation of protein coronas," which would thermally and chemically insulate the particles.

Anikeeva plans to further develop the method to be able to stimulate neurons faster or to stimulate different brain regions independently. But even with the current implementation, the method will be useful—especially for experiments requiring chronic stimulation, as the technique is minimally invasive. In addition, peripheral nerves, which are difficult to stimulate with implanted electrodes, are ideal targets for magnetothermal stimulation.

Nina Vogt

RESEARCH PAPERS

Carvalho-de-Souza, J.L. *et al.* Photosensitivity of neurons enabled by cell-targeted gold nanoparticles. *Neuron* **86**, 207–217 (2015).

Chen, R. *et al.* Wireless magnetothermal deep brain stimulation. *Science* **347**, 1477–1480 (2015).