Using pH to measure brain activity

Functional imaging of the brain has opened new avenues for answering questions about the underpinnings of human behavior. Current methods rely on measuring changes in blood oxygen levels in the brain, which is thought to correlate with neural activity. But now scientists have proposed measuring another factor that varies with brain activity: acid levels.

When neuronal activity increases, pH-lowering lactic acid and carbon dioxide are produced. These pH fluctuations can have dramatic effects throughout the brain by acting on pH-sensitive receptors and channels, which play critical roles in synaptic plasticity, learning, memory, pain and neurodegeneration. John A. Wemmie and colleagues at the University of Iowa in Iowa City have previously shown that increased acidity, or low pH, in the brain is linked with panic disorders, anxiety and depression and that pH fluctuations are associated with normal brain activity as well. However, there are currently no non-invasive ways of measuring pH changes in the brain.

dgstudiodg at iStockPhoto.com

Using a magnetic resonance imaging (MRI) strategy, Wemmie and collaborator Vincent Magnotta have developed a technique that can detect pH changes in the live brain (*Proc. Nat. Acad. Sci.* **109**, 8270–8273; 2012). First testing the method in mice, they systemically manipulated carbon dioxide or bicarbonate levels, which decrease and increase pH, respectively, and used a pH sensor implanted into the mouse amygdala to test the accuracy of their MRI measurements. The MRI-based imaging method was sufficiently sensitive to detect widespread pH changes in the mouse brain just as accurately as the implanted sensor. Later, they instructed a human subject to alter his brain pH levels by changing his breathing rate while in the MRI scanner, and the technique was accurate at detecting these pH changes as well.

Next, the researchers wanted to test the idea that local changes in brain activity could be measured using the pH-sensitive MRI technique just as well as when using methods that measure blood oxygenation levels. When human participants were shown a flashing checkerboard, both the pH-sensitive MRI signal and the blood oxygenation–sensitive signal were observed in the participants' visual cortex.

The scientists argue that pH measurement may be more accurate for quantifying neural activity than the blood oxygenation method, because only the pH-sensitive MRI signal changes in a linear fashion in response to change in pH level. Additionally, the technique is far more spatially and temporally accurate than current methods of measuring brain pH changes, making it crucial to advancing our knowledge of the role of pH dynamics in brain function.

Kara Rosania

STEM CELL TREATMENT FOR MS, WITHOUT THE CELLS?

Multiple sclerosis (MS) is a debilitating neurodegenerative disease that results from an immune system attack on myelin sheaths, the protective outer coatings of axons that are essential for proper communication between neurons. Impairment of myelin and oligodendrocytes, the cells that produce myelin, causes widespread impairments in brain function.

Human mesenchymal stem cells (MSCs), which are derived from bone marrow, appear particularly promising for the treatment of MS because they can modulate both the immune system and neural cell responses. These cells have emerged as a promising approach for stem cell–based therapies for several neurological disorders, because they seem to possess factors that promote repair.

In animal models of MS, treatment with MSCs not only lessens the immune system's attack on myelin and oligodendrocytes, but also leads to myelin repair. A research team led by Robert Miller at Case Western Reserve University (Cleveland, OH) has now shown that medium conditioned with the secretions of human MSCs is sufficient to induce the beneficial effects in a mouse model of MS (*Nat. Neurosci.* published online 20 May 2012; doi:10.1038/nn.3109). The medium itself is able to reduce functional deficits and promote the development of new oligodendrocytes and neurons.

Assuming that something secreted by these cells was responsible for the beneficial effect, the researchers next systematically tested the components of the medium to isolate the powerful substance. They finally identified hepatocyte growth factor (HGF) and its receptor cMet as being crucial to the MSC-stimulated recovery. When the mice were injected with HGF alone, they showed the same improvement in symptoms compared with controls. HGF appears to both block the destructive autoimmune response and repair neuronal damage. Similarly, blocking HGF or cMet prevented the recovery from taking place in the diseased mice.

The improvements that resulted from the HGF treatment were vastly superior to those induced in humans with MS by current treatments, which suppress the immune system from attacking nerve cells but do nothing to repair existing damage. Fortunately, there are several clinical trials testing the efficacy of MSC treatment of MS. This new research could lead scientists to improve the efficacy of this treatment approach by selectively treating patients with cells that produce high levels of HGF. Alternatively, HGF may prove to be an effective treatment on its own, bypassing the complications that can arise with stem cell–based treatments.

Kara Rosania