Evidence found for novel brain cell communication

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An article published today, July 16, 2007, in *Proceedings of the National Academy of Sciences* provides strong evidence for a novel type of communication between nerve cells in the brain. The findings may have relevance for the prevention and treatment of epilepsy, and possibly in the exploration of other aspects of brain functions, from creative thought processes to mental illnesses such as schizophrenia.

The work was performed jointly by scientists at SUNY Downstate Medical Center in Brooklyn, New York; Colorado State University in Fort Collins, Colorado; Mount Sinai School of Medicine in Manhattan, New York; and the University of Newcastle in the United Kingdom. The lead author was Dr. Farid Hamzei-Sichani, an MD/PhD student at Downstate Medical Center, working in the laboratory of Roger Traub, MD, professor of physiology and pharmacology and of neurology at SUNY Downstate.

Epilepsy – a group of disorders characterized by the recurrent occurrence of spontaneous seizures – affects roughly one-half of one percent of the U.S. population, and a higher percentage still in developing countries. In approximately one-third of patients, seizures are not properly controlled by available treatments. Problems can arise in the ability of patients to function at home and in society.

Epileptic seizures are customarily regarded to reflect an imbalance between the ability of nerve cells to excite one another, on the one hand, and to inhibit one another, on the other hand. The excitation and

inhibition take place because the activity of nerve cells leads to the release of particular chemicals – called neurotransmitters – at specialized junctions that are called “chemical synapses”. The neurotransmitters diffuse across a tiny space between the nerve cells, and then bind to proteins (called “receptors”) on other nerve cells. Binding of a neurotransmitter to a receptor in turn causes excitation or inhibition in the other nerve cells.

This is the “classic” means of communication between nerve cells, and lies at the base of most of current understanding of how the brain processes information and controls muscles in the body. A seizure is presumed to occur when there is too much chemical synaptic excitation, and/or not enough inhibition.

There is, however, another means for nerve cells to communicate with one another, called gap junctions. Gap junctions allow electric current to flow directly from one cell to another, without involving the release and diffusion of transmitter chemicals, and may be thought of as “short circuits” linking or cutting across the pathways through which cells normally communicate.

Gap junctions are found in many parts of the body, such as the heart. Gap junctions between nerve cells have been most studied in older vertebrates (such as fish) and in invertebrates (such as leeches and crabs); additionally, gap junctions in mammals have been studied that exist between nerve cells that produce inhibition – that is, between cells that are not primarily involved in epileptic seizures. Gap junctions between excitatory cells in the mammalian brain have not traditionally been part of the thinking of neuroscientists.

One source of the idea that gap junctions were vitally important in epilepsy came from observations of brain waves that are recorded just before a seizure begins: these waves can occur at very high frequencies,

100 times per second or even more. That observation, and other experiments performed in Europe starting 10 years ago, led one of the authors of the PNAS article (Roger Traub, at SUNY Downstate) to propose a novel hypothesis: that excitatory nerve cells – the cells most critical in the generation of epileptic seizures – are also coupled together by gap junctions; that is, gap junctions are not confined to the cells that produce inhibition. Furthermore, gap junctions between excitatory cells were predicted to occur at an unexpected place: the axons of the cells (the axon is the part of the cell that allows propagation of a signal over long distances).

Such an hypothesis was naturally controversial. Scientists wanted to see these proposed gap junctions. But the gap junctions are tiny, and seeing them requires the use of an electron microscope, an instrument able to resolve structural details that are smaller than the wavelength of visible light – details on the scale of tens of Angstroms (an Angstrom is roughly the diameter of a hydrogen atom). Application of the electron microscope to examine tiny structures in nerve cells is a special interest of Dr. Patrick Hof of the Mount Sinai School of Medicine, another of the *PNAS* authors. Furthermore, in the study of gap junctions, use of the electron microscope is often joined with chemical (antibody) techniques that allow one to determine which proteins are present within the junctions. Such techniques were pioneered by Dr. John Rash of Colorado State University, and applied by Dr. Naomi Kamasawa in Dr. Rash's laboratory: both are also authors of the *PNAS* article.

The *PNAS* article by Hamzei-Sichani et al. provides the first electron microscopic evidence (or "ultrastructural" evidence) for gap junctions on the axons of excitatory nerve cells in the mammalian brain. Gap junctions at this site, on axons, would be expected to act as short circuits for nerve signals and to produce "cross-talk." The new data raise the provocative question as to whether cross-talk is an aspect of normal brain function.

What are the implications for epilepsy? First, more needs to be learned about the distribution of gap junctions – what nerve cells have them, where on the cells are they located, and how are they controlled (i.e. can the gap junctions be opened or closed by chemical signals)? Second, more needs to be learned about exactly how gap junctions contribute to the very fast brain waves that can presage a seizure. And finally, it needs to be determined if attenuating or preventing these very fast brain waves can prevent seizures. As is virtually always the case in biomedicine, each discovery creates the need for more experiments.

What is clearly the case, however, is that a whole new direction is opening up in understanding the origins of epilepsy, and in conceiving of new approaches to treatment and prevention.

The classic model of how brain cells communicate was put forth in 1943 by Warren McCulloch and Walter Pitts, at the time the first digital computers were being envisaged, and the McCulloch-Pitts model suggested that brain cells communicate in a binary fashion, represented by a “1” for firing and a “0” for not firing, much as a modern computer functions.

While it is common to say that a mammalian brain functions like a computer, this is a somewhat faulty idea, in part because the observation from the Traub lab suggests that gap junctions cause “short circuiting” as part of the brain’s normal functions. (A real computer could not function if it short circuited.) It is possible that these short circuits in the mammalian brain generally enhance brain function and adaptation to the environment, such as by permitting creative thinking, the combining of isolated facts into new ideas.

Additionally, Dr. Jeremy Coplan, a professor of psychiatry at SUNY Downstate –- has proposed that excessive firing of these circuits along gap junctions may play a role in psychosis and mania.

Source: SUNY Downstate Medical Center