

There has been little research on astrocytes, the stars in the brain's universe. Can basic research on glial cells pave the way for the development of new anti-epileptic drugs?

## Research into glia and epilepsy

Two review articles in this issue of the Journal of the Norwegian Medical Association concern epilepsy. The article *How do anti-epileptic drugs work?* by Karl O. Nakken and colleagues highlights the fact that current epilepsy drugs act primarily on neuronal ion channels and receptors (1). Since one third of patients fail to achieve satisfactory seizure control with monotherapy, it is natural to ask whether glial cells might be alternative therapeutic targets. Kjell Heuser and colleagues summarise research showing that glia, particularly star-shaped astrocytes, are relevant to epilepsy (2). Why have most neuroscientists overlooked glial cells when, in fact, there are more glial cells than neurons in the brain?

The answer may be that for a long time we lacked the technology to capture glial cell activity. Glia do not have neurons' ability to transmit electrical impulses. Ever since Hodgkin and Huxley discovered the action potential 75 years ago, classical electrophysiology has shown glia to be silent when neurons fire. It took the arrival of fluorescence microscopes in the 1990s to reveal that astrocytes can communicate. Synaptic activity increases the Ca<sup>2+</sup>-concentration in astrocytes. These Ca<sup>2+</sup>-signals spread from astrocyte to astrocyte and can, moreover, trigger the release of glutamate and other signalling molecules (called «gliotransmitters») that act on the pre- and postsynaptic terminals of neurons. The concept of the «tripartite synapse» emerged, with reference to the astrocyte as the synapse's third element. Views of astrocyte function changed abruptly. Astrocytes were not just «housekeeper cells», they were also actively involved in perception, learning and behaviour (3).

Over the last 20 years, the number of researchers studying interactions between neurons and glia has steadily increased, and there have been major technological advances. Whereas previously confocal microscopy was used on cell cultures and brain slices, today two-photon microscopy enables researchers to study brain cell activity in living laboratory animals (4). In fact, we can observe synaptic events with millisecond time resolution. New fluorescence indicators are continually being created – a new universe is open for exploration.

Advanced imaging technology alone is not enough to reveal the significance of glial cells for epilepsy and other brain diseases. Imaging of intact brain tissue should be combined with animal models of disease, as well as tools that allow precise manipulation of defined cells. Optogenetics is a promising method where light-sensitive proteins are expressed in target cells and then controlled using light of a specific wavelength (5). The method was named «Method of the Year 2010» by the journal *Nature Methods* and has been used to initiate and to halt epileptic seizures (6). Hardly anyone has applied optogenetics to glia, so this is an area ripe with possibilities. The complex interactions between neurons and glia should also be studied using mathematical modelling.

The discovery of glial cell communication, combined with technological innovations, will lead to a more complete understanding of epilepsy. Animal studies have already shown that signalling molecules from astrocytes can trigger epileptic activity (7). We also know that epilepsy can arise when astrocytes do not fulfil their housekeeping duties. Mutations in the gene encoding the ion channel that astrocytes use to remove potassium from the synaptic cleft can result in epilepsy (8, 9). In temporal lobe epilepsy with hippocampal sclerosis, astrocytic water and potassium channels disappear from membrane domains where they are normally

enriched (the end-feet encircling blood vessels). Animal models show that loss of polarisation takes place before epilepsy manifests itself, disrupting the water and potassium balance (10). Water channels in astrocytes also regulate the drainage of waste from the brain (11). Astrocytes thus function as «cleaning machines» and prevent the accumulation of substances that can damage neurons. This «brainwashing» is most active during sleep (12) – astrocytes have their own nightlife!

We have learned a great deal about glia and epilepsy in a short space of time, but many unanswered questions remain. We lack knowledge of what it is that initiates and regulates epileptogenesis. In many cases, we do not know whether the changes seen in glia are harmful or protective either. It is therefore surprising that the major American research programme «The BRAIN Initiative», featured previously in this journal (13), failed to even mention glia. This omission sparked the commentary «Map the other brain» in the journal *Nature* (14). The author claims that our understanding of glia is a hundred years behind our understanding of neurons. Support for basic research into glia and further technology development will undoubtedly improve our understanding of neuron-glia interactions and help to identify new targets for the treatment of many brain disorders, including epilepsy.

Erlend A. Nagelhus  
e.a.nagelhus@medisin.uio.no

Erlend A. Nagelhus (born 1966) is a professor of physiology with particular expertise in glial cells. He is head of a research group at the Centre for Molecular Medicine Norway and the Institute of Basic Medical Sciences, University of Oslo, and has a secondary position as a researcher in the Department of Neurology, Oslo University Hospital. The author has completed the ICMJE form and declares no conflicts of interest.

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