Dr Christine Ekdahl Clementson is investigating how hippocampal neurons produced after epileptic insult are integrated within existing neuronal networks, and in what ways brain inflammation modulates this process.

How did you become engaged with this line of work? Why do you find it so engaging?

I see research as something natural and important for medical doctors to pursue in order to constantly improve their knowledge of their field of work. As a clinical neurophysiologist I work to a large extent with epilepsy and see the continuous inflow of patients for whom current anti-epileptic treatment is insufficient – this is frustrating! I therefore combine my clinical experience with a genuine interest in understanding how the brain works and reacts to pathological conditions. I’m convinced that there are suitable candidates for therapeutic interventions in the research field of brain inflammation and neurogenesis and I strive to find them!

Why are the pathways between inflammatory cells and neurons, particularly newly formed neurons, considered such promising therapeutic targets?

Epileptic seizures are not routinely treated with anti-inflammatory drugs. Patients with severe epileptic encephalopathies may receive high doses of cortisone or adenocorticotropic hormone treatment, but there are no selective immune-modulating drugs in clinical use. However, there is overwhelming evidence for a strong inflammatory response in animal models of not only epileptic encephalopathies, but also temporal lobe epilepsy, the most common type of epilepsy. In addition, the immune reaction is evident in brain tissue from patients with medical refractive epilepsy who have undergone

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**Enideavours in epilepsy**

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**6 million**

people with epilepsy in Europe
Could you outline why the functional role of adult hippocampal neurogenesis remains poorly understood? What implications does this have?

Most pre-clinical studies on neurogenesis are performed in mice and rats. One obstacle arises due to the relatively limited behavioural tests available for analysing alterations in specific brain functions localised to the hippocampus of rodents. In the clinic, neuropsychological tests for cognition are routinely used on patients, ie. during epilepsy surgery diagnostics or when evaluating dementia. Exploring cognition in rodents is more challenging. Still, cognitive tests for rodents can give important indications for the overall impact of neurogenesis on brain functions localised to the hippocampus.

When studying the impact of neurogenesis in epilepsy, electrophysiological recordings for seizure frequencies and interictal activity are technically relatively easy to perform in rodents and crucial outcome measurements. However, these studies are time-consuming.

Have you encountered any unforeseen challenges over the course of the project? How have these been overcome?

One way to study the expression of synaptic proteins, such as adhesion molecules on individual newly formed hippocampal neurons of different developmental stages in vitro, is to combine stereotactic intracerebral injections of retroviral vector carrying green fluorescent protein (GFP), with high-resolution confocal microscopy on immunohistochemically processed brain tissue. However, manual confocal microscopy of clusters of synaptic protein on individual GFP-stained segments of cell soma and dendrites is much more time-consuming than we had expected. We have not yet fully overcome this problem, but new advances in confocal microscopy seem promising.

With whom are you collaborating, and what value and expertise have they brought?

We are currently working with neurologist Dr Lars Etholm at the University of Oslo, Norway. We are evaluating different immune factors and neurogeneses for their potential as biomarkers in epilepsy. The Oslo group is providing genetically modified mice that develop epilepsy spontaneously and have carried out extensive characterisation of the different seizure types.

How important is public engagement in this field?

There is a strong need to discuss epilepsy and the consequences of epilepsy among the public. Traditionally, seizures are often associated with shame and unwillingness to speak about the disease. Some have other neurological diseases that triggered their epilepsy, eg. asphyxia during birth, stroke, brain infection and dementia. Co-morbidities like depression are common. The seizures per se can sometimes be directly life-threatening; sudden unexpected death is increased in patients with epilepsy. Despite this, funding for the disease is much lower compared with many other neurological diseases. The emerging evidence for immune modulation in epilepsy as future drug therapies may be one way to attract new funders.

Inflammation and neurogenesis following epileptic seizures

Epilepsy consists of a diverse group of neurological disorders characterised by the occurrence of seizures. It affects over 50 million worldwide, mostly in developing countries, and is most common amongst infants and the elderly. It can also occur after head trauma or brain surgery. Drug treatments are often successful at reducing seizure occurrence, but in over 30 per cent of cases even the best medication does not benefit the patient. As such, there is a need to identify new therapeutic strategies and develop novel drugs for the treatment of epilepsy in these instances.

One potential route involves adult neurogenesis – the process by which new neurons arise and integrate within the adult brain. Adult neurogenesis in the hippocampus has been shown to be influenced by many factors, including a variety of pathologies such as epilepsy. Post-seizure, the production of new neurons in the hippocampus has been shown to increase; however, many of these neurons die soon after through apoptosis. Surviving neurons successfully integrate with the existing neural network of the hippocampus, but their impact and function are virtually unknown. An improved understanding of the function of these new neurons, as well as the molecular mechanisms that regulate their integration within the adult brain, will hopefully provide novel therapeutic targets.

Treading new ground

Dr Christine Ekdahl Clementson of Lund University, Sweden is working at the forefront of this field. Her research stretches from the laboratory to the bedside, and has made important and intriguing contributions to epilepsy, neurogenesis and the immune system.

The work is currently structured to address three main issues and aims to conclude in the development of novel treatments that will reduce seizure frequency, prevent seizure development and propagation and treat the cognitive deficiencies that often follow seizures.

The first area of research focuses on the integration of newborn neurons within the hippocampal network after status epilepticus (SE) in the adult brain, specifically looking at the dynamic properties of synapses and the role of adhesion molecules in this context. It is thought that the structure and dynamic behaviour of the dendritic spines on which excitatory neurons synapse may play an important role in the regulation of transmission at afferent synapses. Ekdahl Clementson is using two-photon microscopy to study post-seizure dendritic spine movement and morphology, studying retrovirally green fluorescent protein (GFP)-labelled newly formed neurons as the focus of study. It is hoped that this will provide insight into the role of new neurons with respect to altered excitability in the adult brain after SE. Through this, Ekdahl Clementson has recently shown that newly integrated hippocampal neurons showed altered adhesion at inhibitory synapses and has also started characterisation of related signalling pathways such as those involving the ion co-transporters KCC1 and KCC2. This study is also extended to other adhesion molecules and is investigating their behaviour at different developmental stages to better understand the different roles of adhesion molecules in synaptic assembly, transmission and plasticity.

In the future, the team will modulate adhesion molecule expression and study the effects on dendritic spine motility and synaptic transmission. They also plan to determine the expression of other non-synaptic adhesion molecules, particularly those influencing cell fate commitment and neurite outgrowth.

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INTELLIGENCE

EFFECTS OF INFLAMMATION ON NEUROGENESIS FOLLOWING EPILEPTIC SEIZURES

OBJECTIVES

The primary clinical goal is to identify new treatment strategies for patients with epilepsy through modulation of brain inflammation, neurogenesis and synaptic proteins. Experimentally, the group explores how newborn neurons integrate and function in the epileptic brain, the diversity of the brain inflammation in epilepsy, and how inflammation modulates neurogenesis.

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CHRISTINE EKDAHL CLEMENTSON

defended her PhD in neurobiology at Lund University (2003), and obtained her MD/ licence in 2007. She is a resident in clinical neurophysiology at Skåne University Hospital, and recently started up the Inflammation and Stem Cell Therapy Group which, from this year, shall be financed by the Swedish Research Council.

RESULTS SO FAR

To date, Ekdahl Clementson has made significant progress, having demonstrated that modulation of microglial activation following severe epileptic insult can rescue a substantial number of the new neurons that would otherwise die through apoptosis. By selectively inhibiting different immune system signalling pathways, the researchers have been able to increase or decrease the rate of survival of these new neurons, demonstrating the twin role of brain inflammation for neurogenesis. Such heterogeneity has important implications in the development of new therapeutic strategies.

The longer term impact of neurogenesis after seizures is considerable: without any treatment, surviving neurons constitute ~10 per cent of the hippocampal granule cell layer, with a significant increase in inhibitory activity compared to mature neurons or new neurons that have been produced in healthy tissue.

Ekdahl Clementson’s results imply that new neurons can integrate into the epileptic environment and help to counteract the surrounding hyper-excitible environment. This would suggest that treatments designed to selectively increase the survival of new neurons will be beneficial in epilepsy and could provide an important target for therapy. However, there is evidence to the contrary from other groups, which demonstrates the need for further research in this area.

TRANSLATION TO BEDSIDE

Ekdahl Clementson’s ambitions are geared towards translating these findings to the bedside, identifying therapeutic targets and enabling clinical trials of novel drugs to take place, potentially providing hope for those afflicted by currently untreatable epilepsy: “We are at the stage of evaluating different possible targets suitable for modulation. This means several years of research lie ahead before we might translate it into clinical trials, but we are certainly on the path to doing so”.

Beyond the study of epilepsy, this work also has the potential to build upon current understanding of both neurogenesis and the immune system, and has important implications for stem cell transplantation, where the survival of transplanted cells is variable and crucial to successful treatments.