

Annual Report 2006

Overview of the year

2006 was the first year of funding of LUCENS from the Lundbeck Foundation. Some of the groups already had running projects financed from the Lundbeck foundation or other sources which could be carried on into 2007. Other groups had to start from scratch hiring personnel and creating laboratories. The stroke group is a mixture of a strong ongoing research effort in Professor Edvinsson's laboratories here and in Sweden and the addition of new partners focusing on PDE and on a neurosurgical stroke model.

The Glostrup Research Park was scheduled to be completed by September 1st 2006 but in reality the groups have only been able to move in through the month of December 2006. Work has, however, continued in existing facilities and building delay has only slightly influenced our productivity. In return for the later completion, the research park has been expanded relative to the original plans and the center is now enjoying excellent facilities in top modern laboratories with office facilities in the same building as the laboratories.

Financially we have slightly under spent in 2006 due to the delayed hiring of personnel. This will provide a chance for enhancing particularly promising research in future years. From an administrative point of view, the different routines have been worked out and are now functioning smoothly. The Ph.D. course plan has been somewhat delayed but will be presented in 2007. The meetings of the different groups have been fruitful and the cooperation and mutual support will be greatly enhanced in 2007 when all groups have moved into the research park. External funding has been excellent for most of the participating groups. The most notable example is perhaps the ophthalmologist participant in LUCENS Michael Larsen. He received a chair in ophthalmology at the University of Copenhagen, located at Glostrup and has spearheaded a 22 million Danish crowns grant from Højteknologifonden (on a different theme, but still supportive of LUCENS). Members of LUCENS also received a very significant portion of the grant money donated by The County of Copenhagen for 2006 and 2007. Finally, it should be mentioned that the interest in working within LUCENS has been very considerable. Thus, every position available has been filled by very qualified persons. We envision that this strengthening of our staff in basic science will greatly enhance our collaboration with basic neuroscience groups in other parts of The University of Copenhagen and elsewhere.

Theme I: Neurovascular signalling in migraine

Migraine research has progressed satisfactorily in 2006 despite delayed availability of the new laboratory facilities. The old facilities were sufficient until we expanded our staff with the recruitment of post.doc Saurabh Gupta, who joined us November 1st after having defended his thesis at the University of Rotterdam, The Netherlands. In the month of December we could not do experiments due to the move from the old to the new facilities, but Saurabh was quickly integrated in our group and worked a lot on protocols and future plans. We have decided to delete the project on second messenger signalling in migraine. This is primarily due to the much reduced budget of LUCENS compared to the original proposal. However, due to other external funding we have been able to expand LUCENS with a human migraine project studying the effect of iecosanoids in human volunteers. After a slightly difficult start the MR studies have also developed satisfactorily but they are a bit behind schedule. We have recently established a close collaboration with the imaging group at Massachusetts General Hospital and McLean Hospital in Boston. It has been gratifying to see that 3 new principles for the development of migraine drugs, for which we have been partly responsible, are now being tested in clinical trials. These are: prevention of cortical spreading depression, selective nitric oxide synthase inhibition and CGRP receptor antagonism. We feel that this has demonstrated the utility of our general approach to migraine mechanisms. We therefore continue our studies of substances in humans with increased force to see if they can induce headache and/or migraine and then follow up with animal experiments to analyze where these mechanisms are acting.

Theme II: Neurovascular signaling in stroke

The work on neurovascular signalling in stroke consists of three major groups led by Lars Edvinsson, Jens Astrup and Helle Iversen/Christina Kruuse had initially started in the available and separate surroundings. After moving to The Glostrup Research Park in December we now have optimal physical possibilities for collaborative work. We will share one operation room (present) and this is currently adapted for our needs. The animal models, subarachnoid hemorrhage (SAH) and middle cerebral artery occlusion (MCAO) followed by reperfusion after 2 hours, are being set up by Saema Beg and Gunilla Gidø at the research park. The molecular biology methods and the in vitro pharmacology are working routinely. We have just got a confocal microscope for studies of receptor localization and staff is being trained on the instrument. We foresee an excellent collaboration between our groups with many projects in common. Thus, we have the staff necessary and the methods for performing excellent collaborative work on the vascular receptor changes in stroke models.

Theme III: Structural alterations in schizophrenia. Stability over time and relation to functional deficits

Because of the low financial allocation from LUCENS to Theme III, DKK 200.000 per year, the project has had to be changed as regards both aims and milestones. The project has now been coupled to an already ongoing study in first episode and antipsychotic naïve schizophrenia. In 2006 we have used the first part of the year to redefine the project, to prepare the study and to recruit the PhD student. August 1, 2006, we succeeded to recruit the student, Bjørn Ebdrup, MD. After that time we have started to enrol patients and their controls. Together with the MRI department and as a part of the project we also develop a new method to evaluate sensory evoked potentials (SEP) during sensory fMRI in healthy volunteers to be used later on in schizophrenic patients.

Theme IV: Neurovascular signalling in the eye

Proteomics studies have shown evidence of an adaptation of mitochondrial metabolism to chronic hyperglycaemia. Clinical methods of studying ocular ischemia have been established. The project has been delayed by the translocation of the Department of Ophthalmology from the Herlev Hospital to the Glostrup Hospital. An independent, but thematically related clinical project on ocular ischemia has been initiated. It is intended to merge with the ongoing Lucens project in 2007.

Theme V – Cerebral activity – flow-metabolism relationships

The focus of our work in 2006 has been on synaptic control of local cerebral changes in metabolism accompanying functional activation. We decided already some years ago to develop an experimental model that could assess changes in cerebral blood flow and metabolism evoked activity in neuronal circuits intrinsic to the brain, and has used stimulation of transcallosal fibers for this purpose. We have in 2005 published a paper concerning the CBF and synaptic responses, and have in preparation a paper that compares the changes in oxygen consumption for a small cortical region stimulated by either somatosensory afferents or transcallosal fibers. Interestingly the study provides evidence of large-scale changes in oxygen consumption evoked by the two circuits that evoke approximately the same level of synaptic activity in the targeted region. This suggests that the nature of the afferent input function is an important determinant of metabolic responses, and emphasize that the signaling properties of the activated circuits control both the vascular and the metabolic response to a given stimulus. Along this line of research we have elucidated the effect of cortical spreading depression (CSD) on neuro-vascular and -metabolic coupling in rat sensory cortex. We have analyzed data for up to 1 hour after a CSD, and have observed that the responses of local oxygen consumption as indicated by the dip in the tissue oxygen tension evoked by stimulation of transcallosal fibers in the range 0.5-40 Hz is decreased. Also neurovascular coupling is impaired as described

previously. This in turn has been correlated to the synaptic responses in the wake of CSD, and we have found that the defects of neuro-vascular and –metabolic coupling correlate to the reduction in synaptic activity. To this end we have developed a ‘decrement response test’ as described in detail in the attached document, which is reminiscent of the test we use in the clinical work to determine functional defects of the best studied synapse in the nervous system –the neuromuscular junction. We consider the development of a ‘cerebral decrement response test’ an interesting possibility to probe synaptic function in disease states, and plan to work further with this in 2007.

Theme VI: Human neurovascular signalling and pharmacology evaluated by advanced MR techniques

During 2006 several projects inside the framework of the Lundbeck Centre for Neurovascular Signalling as well as outside have been initiated. We have employed three people, new equipment has been installed, and fMRI data collection has been streamlined. We have implemented several techniques enabling advances on key LUCENS projects, including simultaneous EEG/fMRI, drug delivery or inhalation of gases, electrical somatosensory stimulation, thermal trigeminal stimulation, accurate CBF/CBV measurements, logistics for rapid examination of patients with optic neuritis, and logistics for acute examination of stroke patients. Investigation of neurovascular coupling in somatosensory cortex will be emphasized in our future work. The most notable new equipment is the EEG system from Brain Products, allowing us to perform simultaneous EEG and fMRI. The system was installed in December 2006. So far we have among other things obtained visual evoked potentials (VEP) during visual fMRI in a few volunteers. A setup for drug delivery of pharmaceutical substances or inhalation of gases, e.g. CO₂, inside the MR scanner was implemented, together with appropriate physiological monitoring devices. Available research time on the 3-Tesla MR scanner comprises the whole Monday and Tuesday from 1 p.m. These time constraints mean that research is also taking place in the late afternoon Monday, Tuesday, Thursday and sometimes Wednesday and during weekends. Regarding manpower, to undertake the clinical project on optic neuritis, Dan Fuglø, MD has started as a Ph.D. student on January 1, 2006. Further we have employed Simon Pedersen, physicist, Ph.D., as a post-doc starting from March 1, 2006. His main focus is EEG/fMRI techniques and neurovascular coupling. Both Dan and Simon are fully financed by LUCENS. Furthermore, Helle Simonsen, technologist, having worked in the field of MR research, has been employed at our institution from August 1, 2006, partly financed by LUCENS. We now have 3 very skilled and well-trained technologists available for research purposes.

Overall therefore, we have implemented and established the infrastructure for the MR projects with regards to LUCENS. However, we have been overly optimistic with regards to the expected scientific output proposed in the milestones.