Neuroprotective Interventions and Rehabilitative Strategies in an Animal Model of Ischemic Stroke

by

Rasmus Kragh Nielsen

In Denmark, approximately 12,000 people each year suffer from occlusion of one or several blood vessels within the brain. As a consequence, around 30,000 – 40,000 people are currently suffering from impacts related to stroke incidents. The physiological processes which occur after an ischemic stroke evolve over time and space and are dependent on the severity and location of the ischemia. To further increase the complexity, several of the processes have a 'janus-faced' nature with both beneficial and damaging effects. As a consequence, it is highly difficult to both monitor and predict how ischemia develops, and therefore it has shown to be highly complicated to effectively perform neuroprotective interventions and rehabilitation. In this way, a need for innovative techniques to monitor ischemic stroke as well as neuroprotective and rehabilitative benefits from stroke interventions exist.

The thesis hypothesizes that novel information on ischemic stroke, neuroprotective and rehabilitative interventions can be obtained by monitoring the electrophysiological characteristics of the ischemic brain. To address the hypothesis, four studies were conducted using an ischemic stroke model in rats.

The objective in Study I was to develop and test a novel intracortical microelectrode array and data analysis techniques for use in the ischemic stroke model. The study showed that the ischemic stroke model allowed for detailed investigation of the acute electrophysiological changes that occurred following ischemic stroke due to its high spatial and temporal resolution. Further, the model rendered it possible to monitor the animal directly following ischemic stroke (i.e. in an acute setting) and potentially into the chronic phase.

Study II-III investigated the neuroprotective effect of low-frequency electrical stimulation applied to the ischemic brain in the acute phase. Study II demonstrated that ischemic stroke lead to acute hyperexcitability of the cortical tissues that were most likely located within the penumbra and/or lesser ischemia-affected regions. We found that low-frequency electrical stimulation applied to the ischemic brain reduced the overall amount of hyperexcitability, which suggests that electrical stimulation potentially can delay and reduce the ongoing expansion of the ischemic core. Study III further indicated how hyperexcitability spread along a complex path influenced by time, space and neural connectivity, and that application of low-frequency electrical stimulation minimized this spatial and temporal spreading within the affected tissue.

Study IV explored how the timing of rehabilitation onset affects the regeneration of the affected neural networks. The study indicated that repetitive rehabilitative training initiated at seven days post ischemic stroke resulted in improved motor function performance and neural activity patterns that were more similar to healthy state, compared to initiating rehabilitation on day one post stroke. In this way, the results supported the existence of a critical time window where onset of rehabilitation may be more effective and facilitate a higher degree of neural regeneration.

The present results provided new insights into ischemic stroke and how to time rehabilitation onset, as well as promising results concerning electrical stimulation as a neuroprotective intervention. In this way, the thesis provides a basis for future studies seeking to improve the outcome for stroke patients.

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Ph.D. lecture

by

Rasmus Kragh Nielsen

Monday 24 October 2016

DEPARTMENT OF HEALTH SCIENCE AND TECHNOLOGY
AALBORG UNIVERSITY

This thesis is based on Rasmus Kragh Nielsen's research work at:

SMI
Department of Health Science and Technology
Aalborg University
Denmark

To fulfill the requirements for the Ph.D. degree, Rasmus Kragh Nielsen has submitted the thesis: Neuroprotective Interventions and Rehabilitative Strategies in an Animal Model of Ischemic Stroke, to the Faculty Council of Medicine at Aalborg University.

The Faculty Council has appointed the following adjudication committee to evaluate the thesis and the associated lecture:

Associate Professor Numa Dancause
Département de Neurosciences
Université de Montréal
Canada

Chief Physician Troels Wesenberg Kjær
Sjællands Universitetshospital - Roskilde
Denmark

Chairman:
Associate Professor Carsten Dahl Mørch
SMI, Aalborg University
Denmark

Moderator:
Associate Professor Cristian Sevcencu
SMI, Aalborg University
Denmark

The Ph.D. lecture is public and will take place on:

Monday 24 October 2016 at 13:00
Aalborg University – Room D2-106
Fredrik Bajers Vej 7 D2
9220 Aalborg East

Program for Ph.D. lecture on

Monday 24 October 2016

by

Rasmus Kragh Nielsen

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Chairman:	Associate Professor Carsten Dahl Mørch
Moderator:	Associate Professor Cristian Sevcencu
13.00	Opening by the Moderator
13.05	PhD lecture by Rasmus Kragh Nielsen
13.50	Break
14.00	Questions and comments from the Committee Questions and comments from the audience at the Moderator's discretion
16.00	(No later than) Conclusion of the session by the Moderator

After the session a reception will be arranged