

## REVIEW

# Epilepsy Research in the Institute of Physiology of the Czech Academy of Sciences in Prague

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## Summary

Starting from simple clinical statistics, the spectrum of methods used in epilepsy research in the Institute of Physiology of the Czechoslovak (now Czech) Academy of Sciences progressively increased. Professor Servit used electrophysiological methods for study of brain activity in lower vertebrates, neuropathology was focused on electronmicroscopic study of cortical epileptic focus and ion-sensitive microelectrodes were used for studies of cortical direct current potentials. Developmental studies used electrophysiological methods (activity and projection of cortical epileptic foci, EEG under the influence of convulsant drugs, hippocampal, thalamic and cortical electrical stimulation for induction of epileptic afterdischarges and postictal period). Extensive pharmacological studies used seizures elicited by convulsant drugs (at first pentylenetetrazol but also other GABA antagonists as well as agonists of glutamate receptors). Motor performance and behavior were also studied during brain maturation. The last but not least molecular biology was included into the spectrum of methods. Many original data were published making a background of position of our laboratory in the first line of laboratories interested in brain development.

## Key words

Epileptic foci • Epileptic seizures • Phylogenesis • Ontogenesis • Rat

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Epilepsy research in Prague started before the Institute of Physiology (Czechoslovak Academy of

Sciences) was founded. Young associate professor of neurology Zdeněk Servít formed a group of medical students interested in neuroscience. In this group were among others Jan Bureš, Olga Burešová, Jozef Zachar and Darja Zacharová. When the original Institute of Biology of the Czechoslovak Academy of Sciences was divided into three independent institutes, Zdeněk Servít became the director of the Institute of Physiology. The group continued its action for some time [1,2], then Zachars left for the newly established Slovak Academy of Sciences in Bratislava. Jan Bureš formed his own group and prof. Servít continued with new collaborators (e.g. Jiří Machek, Jaroslav Šterc, Alena Štercová, Libuše Chocholová, Věra Nováková, Zdeněk Lodin and others). The official names of the laboratories corresponded to the political situation – Department of Central Excitation (epilepsy research) and Department of Central Inhibition (Bureš' lab studying spreading depression). One of the models frequently used in the laboratory were audiogenic seizures [3-8].

The new people in the Servít's laboratory – outstanding neurophysiologist Josef Holubář and neuropathologist Jindřich Fischer – extended the spectrum of methods [9-10] and started to study cortical epileptic focus elicited by cobalt implanted into cerebral cortex of rats [11-17]. Unfortunately, Josef Holubář died in a car accident in autumn 1967. Professor Servít studied epileptic phenomena during phylogenesis [18-20]. In this research were involved Alexandra Strejčková (originally technical assistant, later successful absolvent of Faculty of Natural Sciences of the Charles University) and for some time also Dan Volanschi from Romania [21-31].

Zdeněk Servít, who became full time professor at the Faculty of Pediatrics (Charles University), was also active in the Czechoslovak Academy of Sciences and was promoted from the corresponding member to the regular Member of Academy. He never left clinical epileptology and on the background of his older experimental data [32] he published an important paper in collaboration with a clinical neurologist assoc. prof. František Musil [33]. This paper provoked U.S. epileptologists to make a big study in soldiers with head injuries from the war in Vietnam. This extensive study made a conclusion that prophylactic treatment is important in people with serious brain injuries but it is not necessary in patients with simple brain contusion. Professor Servít continued his clinical studies in collaboration with an experienced neurologist Miroslav Křištof and their topic was the activation of epileptic phenomena by nasal hyperventilation [34-37].

I entered Servít's laboratory in September 1967 and Professor Servít wanted to involve me in phylogenetic studies. At the entrance presentation I showed my results from ontogenetic studies of visual and somatosensory evoked potentials in rats and immediately after this presentation prof. Servít decided that we will study phylogenetic and ontogenetic development in parallel. My developmental orientation was thus approved and I could continue in the research, which started during my student years at medical school.

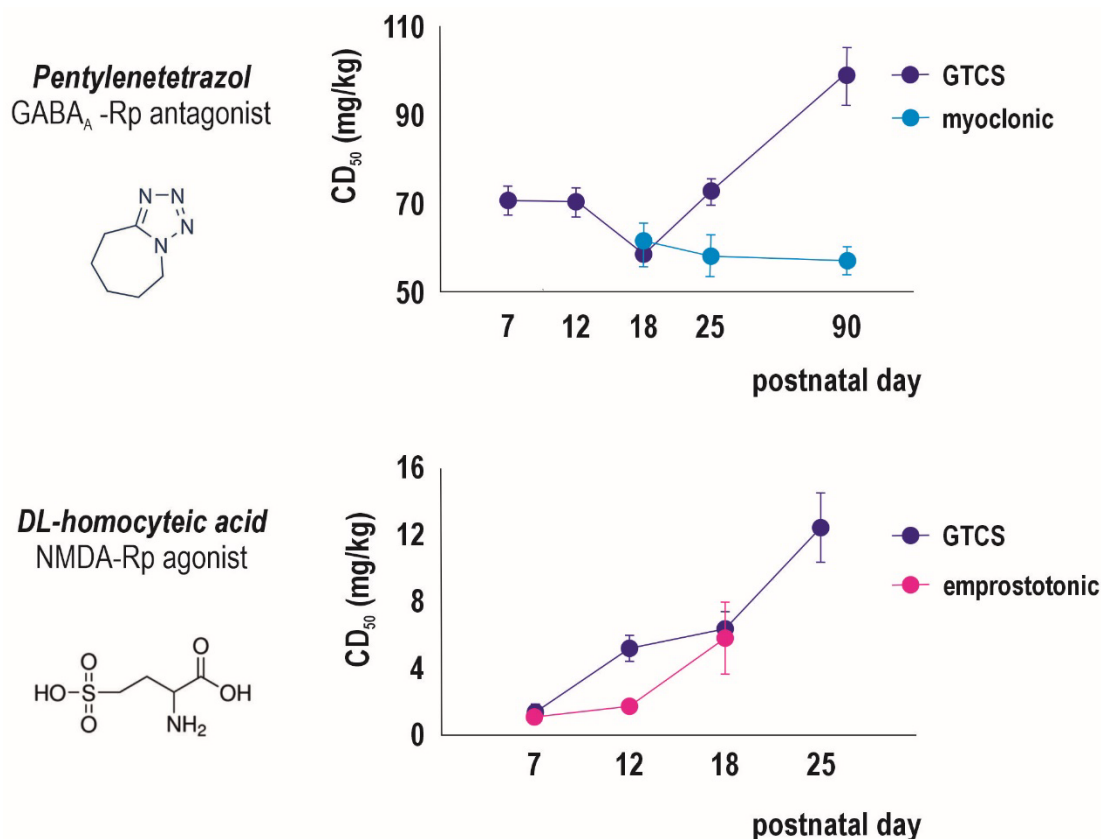
Further development was affected by political events. After hopes of Prague Spring came September 1968. Professor Servít refused to annulate his signature under the manifest „*Two thousand words*“ qualified by the new government and by the leadership of Czechoslovak Academy of Sciences as an anticommunist manifest. He was progressively withdrawn from his positions and finished as a regular scientist. His employment was prolonged always only for one month. This was contrary to the existing law according to which the employee with time-restricted contract must be informed three months before the end of the contract whether it will or will not be prolonged. The employment of prof. Servít in the Institute of Physiology was preserved thanks to his medical practice – some of his patients were in “good” positions in the communist party. After a certain (not short) time his employment was prolonged for six months and then repeatedly for one year. The only Servít's position preserved was the Member of Academy because this title might be withdrawn only if the scientist was participating in

a criminal action. However, at that time the emigration to West was qualified as a crime for which several Members of Academy were stripped of their title.

Professor Servít was also withdrawn from the leadership of the laboratory and it was necessary to have a new head of the laboratory. We proposed Jindřich Fischer to Ladislav Vyklický (at that time a temporary head of the institute) and he accepted this proposal.

Studies of epileptic seizures continued in the laboratory but individual scientists had their own topics and only occasionally collaborated. Professor Servít with Dr. Strejčková continued in the studies of epileptic foci in amphibia and reptiles and published their results mostly in *Experimental Neurology*, which was one of the leading neuroscience journals at that time. Professor Servít also continued his clinical activity not only by seeing patients but also by performing some clinical research [34-37]. Jiří Machek studied the role of potassium ions in direct current potentials of cerebral cortex [38-41], Libuše Chocholová was interested in cobalt foci [42,43] and pharmacology of hippocampal and cortical epileptic afterdischarges in rats with chronically implanted electrodes [44-46]. Jindřich Fischer continued in electron microscopic studies of semichronic cortical epileptic foci elicited by the implantation of aluminium hydroxide into cerebral cortex. He demonstrated important changes in neurons and astroglial cells [47-54]. Original findings were published with the model of cortical stimulation in collaboration with Jan Mareš [55-58]. Later he changed the model for epileptic foci elicited by local application of penicillin on cerebral cortex and in this method we met and published a common paper [59]. His excellent morphological results were published in good journals but the impact of these results was much smaller than they deserved.

Jindřich Fischer died unexpectedly during Christmas 1980. Professor Radil tried to include our laboratory into his department, but he did not succeed and I was established as the head of the laboratory. I started in the Institute of Physiology with studies of the ontogeny of cortical penicillin foci, especially of projection into the contralateral hemisphere including synchronization of symmetrical penicillin foci [60-62]. The research of this topic continued in collaboration with my student Jan Mareš (later associated professor at the Department of Physiology of the Faculty of General Medicine) and we used also cortical stimulation to elicit transcallosal responses and cortical epileptic afterdischarges [63-65]. Model of cortical epileptic afterdischarges is used in our



**Fig. 1.** Fifty-percent convulsant doses of pentylentetrazol (upper part) and homocysteic acid (lower part). There are two types of seizures in either graph: generalized tonic-clonic (GTCS) and minimal clonic (myoclonic) seizures in pentylentetrazol graph and GTCS and emprostotonic (flexion) seizures in homocysteic acid graph. For both graphs: x-axis – age in days; y-axis – doses in mg/kg.

laboratory up to now mostly in pharmacological experiments. Spectrum of epileptic seizures studied was extended by chemically elicited seizures, mostly by subcutaneous administration of pentylentetrazol [66-69] (Fig. 1). This model is generally accepted in the pharmacology of antiseizure medications.

Personal composition of the laboratory changed after the death of Dr. Fischer. Jiří Machek left the institute and Marie Kolínová, who started after finishing the medical school to work with me and Libuše Chocholová, decided to go into neurological practice. PhD student of the late Jindřich Fischer, Miloš Langmeier, finished his PhD study under my formal tutorship and continued morphological studies of consequences of epileptic seizures [70,71]. After a short time he was attracted by academic career and left us for the Department of Physiology of the First Medical Faculty, where he successfully defended dissertation to become associate professor and later he was promoted to the full professor. Collaboration with this Department of Physiology (Jan Mareš, Dana Staudacherová-Marešová,

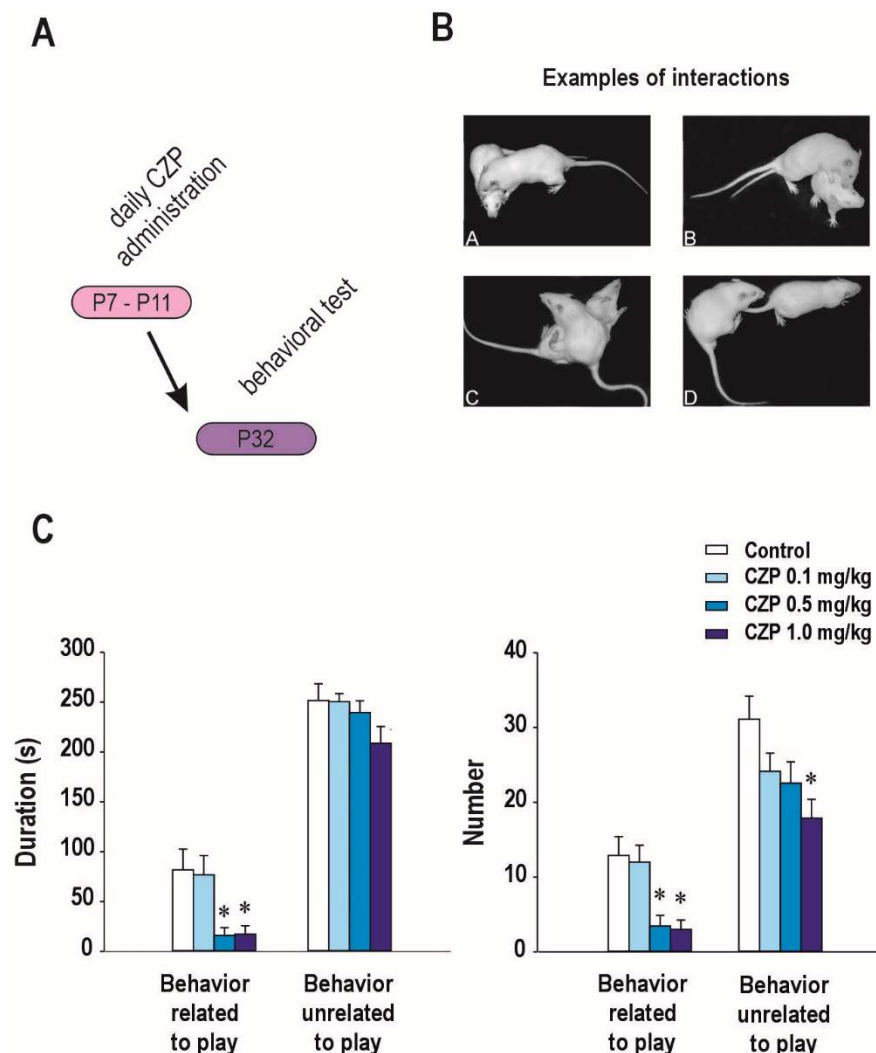
René Schickerová) continued and all these three students finished and defended PhD Thesis under my informal tutorship. René Schickerová then decided for clinical neurology and left basic research. There were many pregraduate students in our laboratory, their results were published and all of them continued their career in neurology or psychiatry – they were imprinted with neuroscience.

In 1988 I started an extra part time job as a head of Department of Pathophysiology of the Third Medical Faculty. I spent there seven years and two of my assistant professors (Klára Bernášková and Iveta Matějovská defended their PhD Thesis under my tutorship. My pregraduate student Michal Pohl finished the Faculty of General Medicine and started PhD study under my tutorship. Among other features of epileptic seizures he studied a possible role of thalamus in generation and spread of epileptic seizures using spreading depression as a tool [72-74]. Another pregraduate student Libor Velíšek also decided to stay in basic research. He entered the pharmacological program with a focus on the antagonists

of glutamate receptors [75-80]. We published a possibility to elicit flexion convulsions by N-methyl-D-aspartate [81]. This model was later used as a background for studies of severe epileptic encephalopathies of early age. In 1990 after defending her PhD thesis at Faculty of Pharmacy of Charles University Hana Kubová came to the laboratory and she worked in the field of developmental pharmacology [82-91]. In collaboration with Professor Rastislav Druga from the Second Medical Faculty she also studied morphological consequences of status epilepticus induced in immature brain [92,93].

Future of the laboratory seemed to be optimistic with three young collaborators (Pohl, Kubová, Velíšek). In a short time the situation was completely changed: Michal Pohl left to a pharmaceutical company, Libor Velíšek started his postdoc stay in the Laboratory of

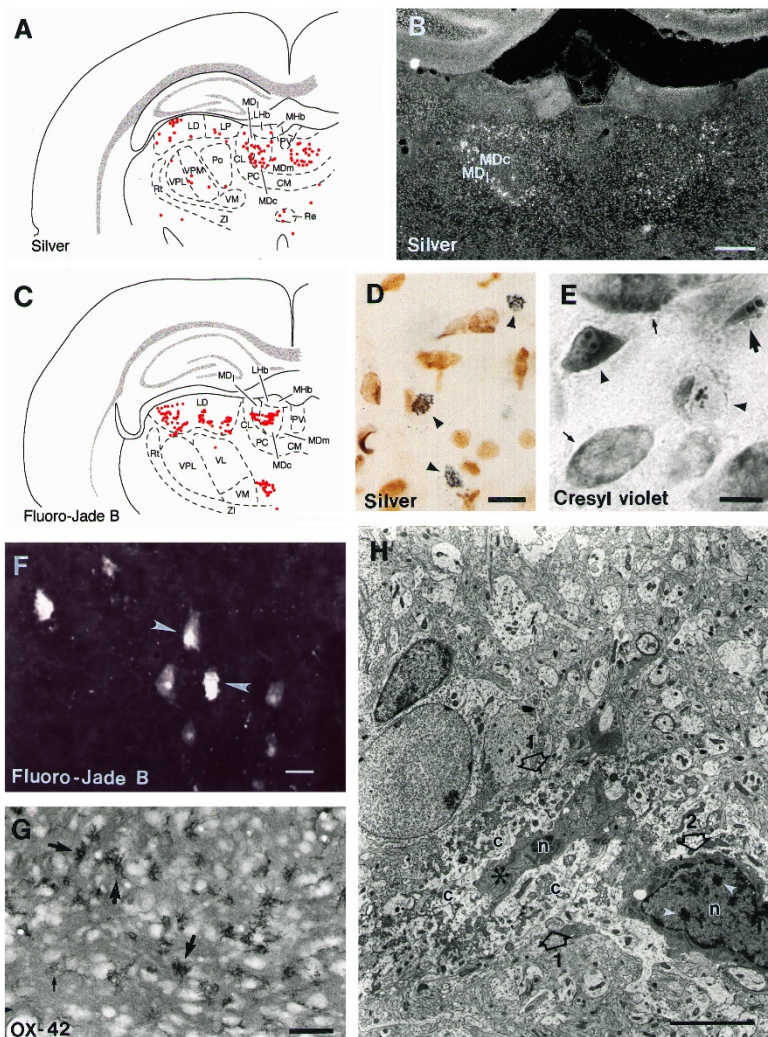
Developmental Epilepsy at Albert Einstein College of Medicine in New York (prof. Solomon L. Moshé) and Hana Kubová went to the same laboratory two years later. There were also some positive changes, because Nina Mikulecká from the Laboratory of Ethology came into our laboratory. She started behavioral studies and modified many tests for immature rats [94-103] (Fig. 2). From the canceled laboratory of František Šťastný came Jaroslava Folbergrová and Renata Haugvicová. Jarka Folbergrová was an experienced biochemist with her own experience in the field of epilepsy and continued in her research on the role of glutamate receptors in epileptic seizures [104-110]. Renata joined the pharmacological developmental program and participated in many studies [111-118].



**Fig. 2.** The repeated administration of benzodiazepine clonazepam (CZP) to immature rats results to long-term alterations of the social interaction including the play behavior in pubescent rats. CZP was administered daily starting at postnatal day (P) 7 till P11 and animals were tested at puberty onset (P32) (scheme of experiment is shown at panel A). Play behavior was suppressed in CZP-exposed animals by dose-dependent manner (panel C). Examples of social interaction are demonstrated at panel B (A) pouncing, (B) wrestling, (C) pinning, (D) following. Modified from Mikulecká *et al.* [100].

From 1994 I served as a deputy director of the Institute of Physiology. In 1995 the Director of the Institute Professor Ošťádal abdicated due to his serious health problems. I was established as a temporary head of the Institute and after two months I was regularly elected to be a director. I did not want to have two relatively high positions and therefore I finished my activity at the Third Medical Faculty. I recommended Libor Velíšek, who came back from USA to replace me in the Department of Pathophysiology. He stayed there for more than one year and then he came back to USA because his wife Jana with children refused to return to Prague. We thus lost a possibility of collaboration and friendly competition in the field of developmental epilepsy. Before the second Libor's leaving to USA Hana Kubová came back and continued in the collaboration with Professor Druga [119,120] and started a collaboration with Professor Asla Pitkanen from Kuopio. This collaboration lasted more than 10 years and led to a number of outstanding publications mostly on the consequences of status epilepticus elicited in immature rats [121-123]. One of

their common papers demonstrated for the first time that status epilepticus elicited in rats less than two weeks old resulted in neuronal degeneration in thalamus (Fig. 3). This collaboration ended when Asla Pitkanen focused her research on posttraumatic epilepsy, while our laboratory continued to study status epilepticus elicited by pilocarpine. Among postgraduate students Pavel Kršek defended PhD Thesis on nonconvulsive status epilepticus [124,125] and then left for the Department of Child Neurology at the Second Medical Faculty. Today he is the head of this department and continues to study childhood epilepsies in clinics. Lucie Suchomelová (postgraduate student of Hana Kubová), who defended her PhD Thesis little later, left for postdoc to the laboratory of Professor Claude Wasterlain in University of California in Los Angeles. It was a start of a collaboration (mostly Hana's) with Claude who was also involved in experimental studies of epilepsy in immature brain [126,127]. This collaboration lasted up to 2023 when Prof. Wasterlain was retired.



**Fig. 3.** Early life status epilepticus-induced neurodegeneration in the mediodorsal thalamus. Status epilepticus (SE) was induced chemically in P12 rats. The distribution of degenerating neurons is demonstrated in the computer-generated plots (A and C). Degenerating neurons were detected using silver staining (B and D), Fluoro Jade B staining (F) and cresyl violet staining (E) 48 h after SE. Panel (G) illustrated activated microglia surrounding degenerating neurons. The presence of irreversibly damaged neurons was confirmed by electron microscopy (H). Modified from Kubová *et al.* [121].

Přemysl Jiruška, a postgraduate student of Professor Brožek, asked me to be his tutor after Brožek's death. He finished his PhD Thesis and after the successful defense he left for United Kingdom (Department of Physiology in University of Birmingham led by Professor John Jefferys). There he spent four years and published some very good papers mostly on fast EEG frequencies and their role in epileptic seizures and epileptogenesis [128-131]. He came back after a drastic reduction of money for universities in the United Kingdom and continued in our laboratory with the analysis of EEG [132-135]. In 2021 he left the Institute of Physiology and became head of Department of Physiology in Second Medical Faculty of Charles University where he continues in epilepsy research. In 2001 Jakub Otáhal entered our laboratory and became fully involved in the study of epileptic seizures and their consequences utilizing his experience with brain hypoxia [136-143]. His collaboration with Jaroslava Folbergrová resulted in a series of excellent papers [144-148]. He also had four PhD students, two of them finished and defended their PhD Thesis (Carol Brožíčková and Tufi Brima) [149,150].

Two girls started their PhD studies under my (Denisa Lojková) and Hana's (Adéla Máteffiová) tutorships and successfully finished their PhD studies [151-155]. A little later Grigoryi Tsenov came from Ukraine, absolved PhD studies [156-158] and stayed for some time in the laboratory before he went to Italy to make his postdoc in Verona. After coming back to Prague he took a position in National Institute of Mental Health and till now he has a small collaboration with our laboratory.

In the meantime I started to lecture basic neurophysiology for physiotherapists and nearly each year at least one student prepared bachelor or magister thesis on motor development of rats and possibilities to affect this development by antiseizure medication or by treatment with agonist or antagonist of various mediator systems [102,159]. The result of collaboration with Professor Jana Tchekalarova from Sofia was a series of papers on possible effects of caffeine postnatal administration [160-168]. It was in accordance with our program because one of the topics in the laboratory was the role of adenosine in epileptic seizures [169]. PhD student Petr Fábera prepared his PhD Thesis in this field [170,171]. In relation to the role of adenosine in the arrest of epileptic seizures we started to study changes of excitability after epileptic seizures [172-175].

Hana Kubová started collaboration with CEITEC and Masaryk University in Brno (prof. Milan Brázdil) on microRNA and their regulatory role in epilepsies [176,177] (Fig. 4). We also began collaboration with neurosteroid group of Eva Kudová (Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences) and with Karel Valeš from National Institute of Mental Health in the field of neuroactive steroids. This collaboration up till now resulted in three common publications [178-180] and a patent. In this collaboration we are using not only pentylenetetrazol-induced seizures but also a new model of temporal epileptic seizures – seizures elicited by transcorneal 6 Hz stimulation. In this field we started collaboration with Department of Pharmacology, University of Utah, Salt Lake City (Cameron S. Metcalf) and the first common publication is submitted.

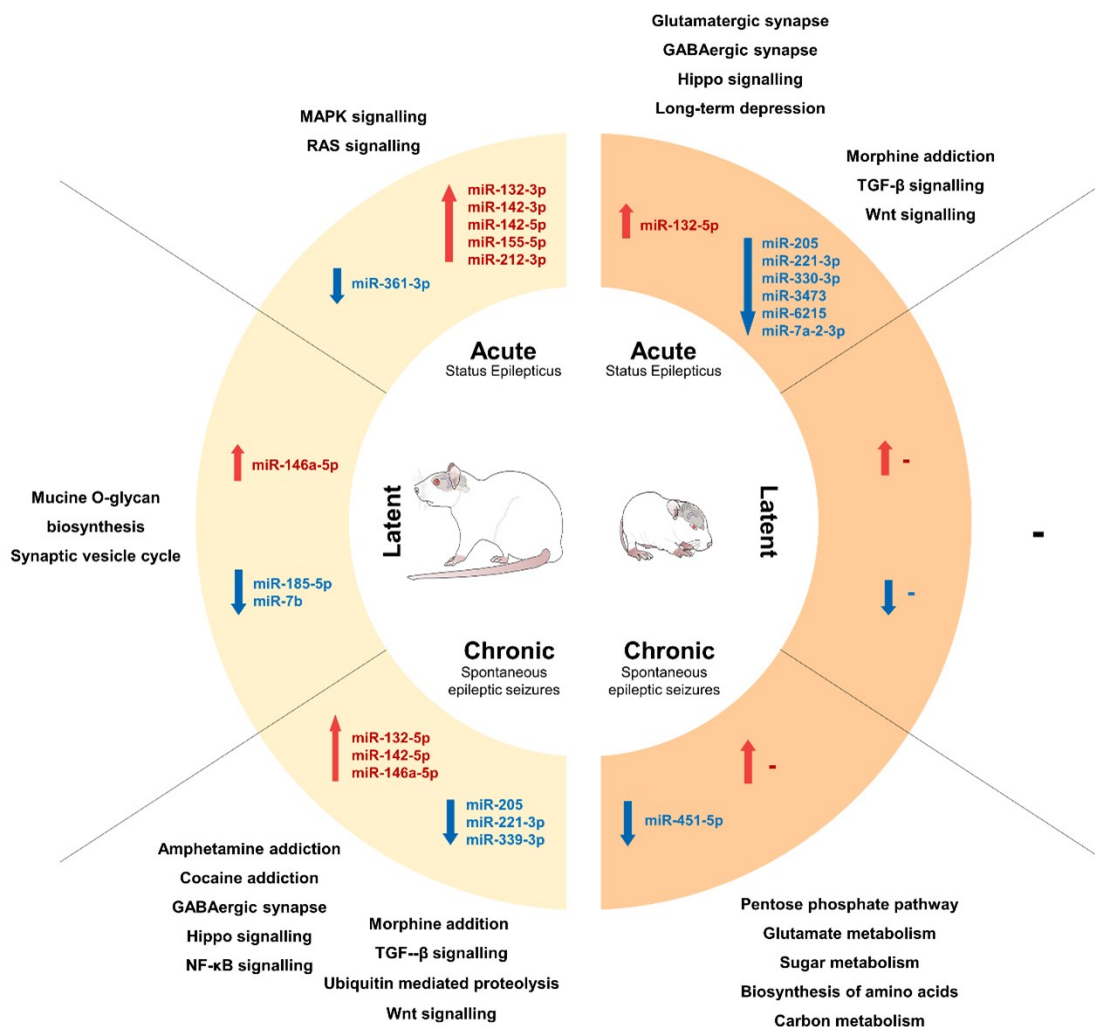
Present situation in the Department of Developmental Epileptology is not optimistic. The department is old but still producing good publications. On the other hand, many our former PhD students continue in epilepsy research at their new leading positions. Another positive fact is that Czech experimental as well as clinical epileptologists publish their results in high quality international journals.

### **Conflict of Interest**

There is no conflict of interest.

### **Acknowledgements**

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**Fig. 4.** The overview of dysregulated miRNAs after status epilepticus (SE) induced in adult (adult rat) and infant (rat pup) rats. The inner parts specify the stage of epileptogenesis with a short description of seizure occurrence. The middle parts contain the lists of dysregulated miRNAs in the respective stages. Upregulated miRNAs are displayed in red, while downregulated miRNA after SE are shown in blue. The outer parts list the predicted pathways affected by dysregulated miRNAs in the given stage. Modified from Bencurova *et al.* [176].

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