Project presentation

Project number

LSHM-CT-2005-019055

Acronym

EUSynapse

Project name

From molecules to networks: understanding synaptic physiology and pathology in the brain through mouse models

Priority/Strategic objective

Life Sciences, Genomics and Biotechnology for Health / Studying the Brain and Combating Diseases of the Nervous System

Project logo

Financing

Total cost: 9,302,904 Euro
Commission funding: 8,000,000 Euro

Duration

48 months

Starting date

01/12/2005

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Summary

The involvement of synapses in many neurological diseases (synaptopathies) is becoming increasingly apparent in recent years. Yet, despite considerable advances in our understanding of synaptic signal transmission processes, much remains to be delineated with respect to the molecular details.

Our aim is to further our understanding of synaptic function using multiple systems. Starting from cell free systems (*in vitro*) we also want to take full advantage of genetically modified mice (*in vivo*), particularly those serving as models for synaptic dysfunction in neurological diseases.

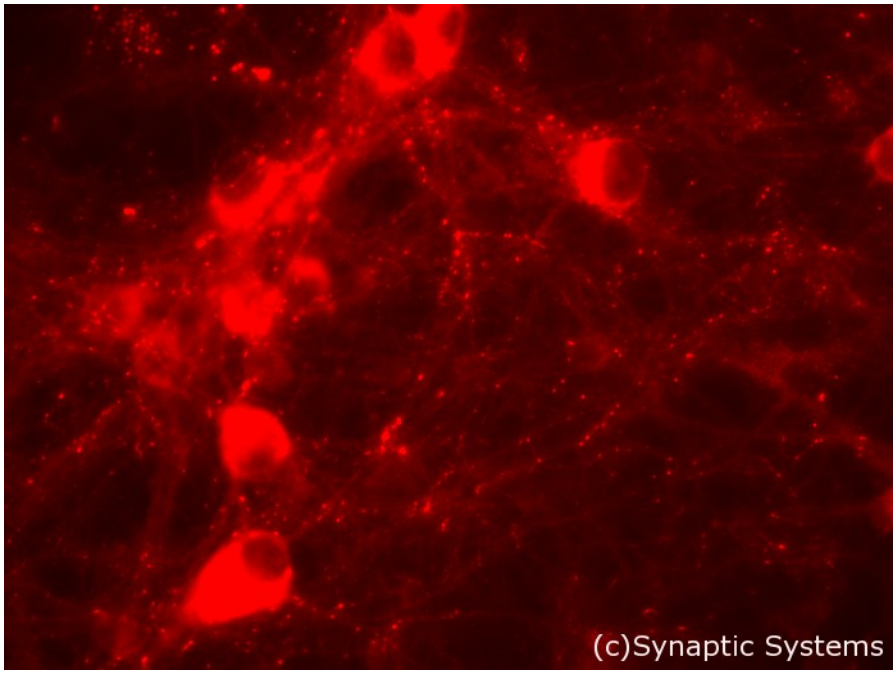
Innovative and state of the art technologies will be applied and optimised, including biochemical, molecular, electrophysiological, and optical tools. We will derive detailed knowledge of molecular machineries that drive synaptic transmission and of mechanisms responsible for changes in the synaptic properties (synaptic plasticity).

We expect that these studies will provide invaluable insights into synaptic function and dysfunction and their contribution to complex brain functions in health and disease.

Problem

Neurological and psychiatric disorders are among the most prevalent and debilitating diseases of modern societies. Most of these, prominently including Alzheimer's and Parkinson's disease, epilepsy, schizophrenia, stroke, chronic pain, and dementia are long-lasting diseases, incapacitating afflicted people for years and even decades, which results in human suffering and immense socio-economic costs. It is becoming apparent that seemingly complex diseases can often be traced to the dysfunction of single or very few molecules. An increasing list of neurological disorders is caused by mutations in proteins, either directly causative for the disease process or increase the susceptibility for developing clinical symptoms. The European Commission has recently underlined the urgency of research in one of he most central areas of neurosciences where connection to diseases is evident but not well understood at the mechanistic level. While it is a long way from understanding the cause of a disease to an effective treatment, it is clear that therapeutic strategies can be developed only by research aimed at an in-depth analysis of the aberrant proteins and their impact on the hierarchy of simple and increasingly complex neuronal functions.

An international consortium of renowned scientists and small and medium enterprises (SMEs) have joined forces to assist the European Commission in addressing and solving the problems outlined above. Significant progress is anticipated during the duration of four years, thus getting closer to the overall goal of combating and treating neurological and psychiatric disorders that arise from synaptic dysfunction.



Unravelling the molecular details of synaptic processes is the mission of the EUSynapse project: A new antibody labels the vesicular GABA Transporter vGaT in cultured neurons

Aim

The overall aim of the project is to build on the treasure trove of information provided by the complete genome sequences of humans and other species. It is one of the major goals to stimulate and sustain multidisciplinary and basic research in order to underpin applications to human health. Both forward and reverse genetic approaches have been immensely facilitated by the availability of genomic databases, affecting virtually all fields of life sciences.

The EUSynapse consortium will significantly further the understanding of synaptic function by using the mouse as the prime model organism. Based on the ability to manipulate the expression levels of synaptic proteins, their role in synaptic transmission and in more complex brain functions will be better understood, providing links to human diseases and identifying candidate drug targets for therapeutic intervention in synaptopathies. Major milestones include

- Development of novel optical methods, generation of reporter mouse models, and the adaptation of preexisting high-resolution techniques (capacitance patch clamping, multiple electrode recordings) to mouse preparations.
- Establishment of genetic procedures to manipulate protein expression levels in mouse model synapses, complemented with proteomic and DNA-array analyses to monitor changes induced by altered expression.
- Determination of the mechanisms by which active zones and postsynaptic densities (PSD) are assembled, taking advantage of mouse models containing key proteins of active zones and PSDs tagged to fluorescent proteins.
- Identification of genes involved in autism, bipolar disease, schizophrenia and language disorders using material derived from human patients. Initial characterization of the role of the candidate genes in synaptic function by introducing mutations/changing expression levels in the mouse.
- Determination of the calcium dynamics and calcium dependent molecular dynamics in the presynaptic terminal. Development of standardized screening assays for identification and quantitation of presynaptic protein complexes.
- Refinement of techniques to measure short term plasticity, and application of these techniques to mouse models with synaptic phenotypes.
- Determination of the rules of assembly, polarized trafficking and signal transduction during physiologically relevant network activities.
- Development of new approaches to study the function of small neural networks in mice, using one sensory and two cortical regions as models. Transgenic reporter lines will be used to identify neuronal subpopulations.

Expected results

The work of the consortium will make significant contributions

- by identifying synaptic genes that are likely to cause neurological disease caused by pathology of synaptic proteins
- by generating mouse mutants that copy genetic aberrations associated with human disease (e.g. deletion mutants lacking neuroligins or complexins)
- by generating and characterizing mouse mutants affecting proteins that result either in a phenocopy of a disease or at least mimic certain aspects of a disease.

Furthermore, standardization of techniques for studying synaptic function will be directly applicable both for diagnostics and the screening/evaluation of potential therapeutics

- by providing standardized assays for expression profiling that are applicable for biopsy material and that may be further developed into standardized diagnostic kits.
- by providing standardized synaptic preparations for the measurement of synaptic parameters that can be utilized for testing drug effects on synaptic transmission
- by developing criteria, used in cell-based or in vitro assays, to screen for neurological side-effects of candidate drugs.

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