The role of axon guidance molecules in synaptic functions

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Title of project or programme

Title of PI The role of axon guidance molecules in synaptic functions

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- Netherlands

Source of funding information

Netherlands Organisation for Health Research and Development (ZonMw)

Total sum awarded (Euro)

675000

Start date of award

1-6-2009

Total duration of award in months

48

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

semaphorin; axon guidance molecules; synaptic plasticity; synapse; connectivity; mental disorders; patch-clamp; proteomics

Research abstract in English

Studying the fundamental process of synaptic plasticity may further our understanding of synaptic

dysfunction in disorders such as Alzheimer’s, schizophrenia and autism and may provide novel therapeutic targets. This program takes a conceptually and technically new approach to define the molecular regulation of synaptic plasticity by proposing a multidisciplinary study aimed at unraveling the role of a novel family of synaptic molecules, the Semaphorins.
The proposed program brings together three Dutch neuroscientists to generate a unique framework for addressing the roles of Semaphorins in the complex process of synaptic connectivity and plasticity. We will take a comprehensive and multidisciplinary approach of biochemistry, molecular biology, neuronal cell biology, electrophysiology and mouse behavior to elucidate the synaptic functions of Semaphorins.
The first key objective is to identify which of the Semaphorin and Semaphorin receptor family members (Plexins) are involved in hippocampal synaptic plasticity. By individually blocking Semaphorin receptor/ligand function in neurons, we will determine their effect on synapse development, maturation and maintenance.
The second key objective is to identify signaling components that function downstream of Semaphorin-receptors at the synapse. Immunoprecipitation experiments coupled to mass spectrometry analysis will be used to identify known and novel components of synaptic Semaphorin-receptor complexes. In addition a combination of small molecule inhibitors and negative approaches will be used to test for known components of Semaphorin receptor signaling.
The third key objective is to investigate the synaptic mechanisms underlying Semaphorin functions in hippocampal plasticity and learning. We propose to test the effect of Semaphorin signaling on synaptic plasticity by combining electrophysiological recordings with live imaging of post-synaptic neurotransmitter receptor behavior and pre-synaptic vesicle trafficking and release. Ultimately, we will use conditional Semaphorin knock-out mice to study the molecular mechanism of Semaphorin signaling in vivo.
Together, this program is expected to generate new insights into the molecular control of synaptic development and plasticity. Such knowledge will significantly contribute to our understanding of neurological and psychiatric disorders and may provide new strategies for improving treatment of these disorders.

Lay Summary
In which category does this research fall?

- Basic research