

Angiopoietins and their Tie receptors in hippocampus neuronal networks and connectivity

Förderprogramm 2014 Schram Stiftung

Dr. Carmen Ruiz de Almodóvar Egea
Biochemistry Center (BZH)
University of Heidelberg
Im Neuenheimer Feld 328
69120, Heidelberg

Tel: +496221544750
Fax: +496221545341

Angiopoietins and their receptors are well known for their function in building and maintaining a functional vascular system. We hypothesize that hippocampal network formation occurs via an orchestration of signals coming not only from the already known neuronal factors but also via vascular cues, which together, assure the highly and stereotypic neuronal and axon patterning required for proper connectivity and function of the hippocampus. This proposal aims to investigate the role of Angiopoietins and their receptors (Tie receptors), in hippocampus neural network formation and wiring.

The hippocampus, a major component of our brain, plays important roles in the consolidation of memory and spatial navigation. Different neuronal cell types are organized in different layers and regions within the hippocampus and form defined neural networks and connections to assure proper and highly precise neuronal activity. Thereby, the correct wiring between hippocampal neurons during development is crucial for the generation and control of specific neuronal activity patterns, which are required for proper function of our brain and which are impaired in situations of memory loss or other neurodegenerative disorders. Despite the fact that the hippocampus is one of the main studied structures in the mammalian brain, it still remains unknown the entire set of molecular mechanisms that regulate their development.

Even though they have distinct functions, the nervous and vascular systems share many more similarities and common principles than previously anticipated. For example, blood vessels and nerves grow in a similar manner. Moreover, recent evidences show that vascular factors are expressed in neural cells and participate in diverse neuronal processes during development and in the adult brain. This new concept, **termed the Neuro-vascular link**, highlights the significance of a shared-tight molecular regulation between the vascular and the nervous system and underlines the importance to study the function of vascular molecules within the nervous system. In this project we will focus on Angiopoietins and their Tie receptors.

Indeed, we have observed that Angiopoietins and their receptors are not only present on vascular cells within the developing hippocampus, but also on neuronal cells. Therefore, we aim to know:

- a) Whether hippocampal neurons morphology is changed in the presence or absence of Angiopoietins signaling
- b) Whether hippocampus development, wiring and connectivity is impaired in the absence of Angiopoietins or their receptors
- c) The molecular mechanisms of Angiopoietin signaling at a single cell level

Our experimental approaches will comprise *in vitro* (cell culture), *ex vivo* (organotypic hippocampal cultures) and *in vivo* (mouse experiments) methodologies using gene targeting technologies, mouse genetics and state of the art microscopy, which integrated together, will give clear results on the importance of Angiopoietins in hippocampal neuronal connectivity.

Findings from this project will broad our understanding on neural network formation and might suggest new therapeutic approaches for the treatment of neurodegenerative disorders where the hippocampus is affected.

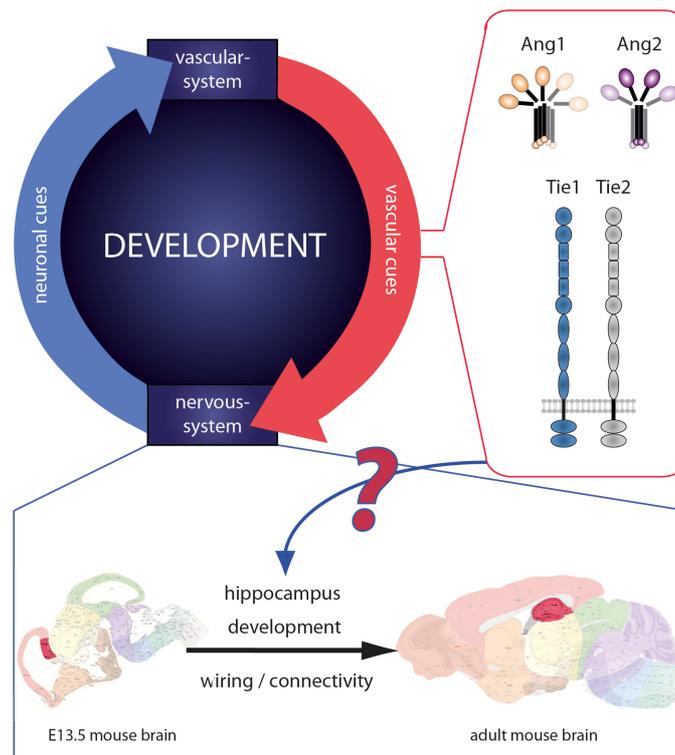


Figure: Scheme summarizing the rationale and aim of this research project. Exploring the functional role of the vascular cues Angiopoietins and their Tie receptors in hippocampus wiring and connectivity during development using the mouse hippocampus as a model system.

Hippocampus anatomy images obtained from Website: ©2013 Allen Institute for Brain Science. Allen Developing Mouse Brain Atlas. Available from: <http://developingmouse.brain-map.org>.

E13.5: [http://atlas.brain-map.org/atlas?atlas=181276130 - atlas=181276130&plate=100792991&structure=16382&x=3684.0006510416665&y=2752.000041923138&zoom=-3&resolution=8.00&z=6](http://atlas.brain-map.org/atlas?atlas=181276130-atlas=181276130&plate=100792991&structure=16382&x=3684.0006510416665&y=2752.000041923138&zoom=-3&resolution=8.00&z=6)

Adult: [http://atlas.brain-map.org/atlas?atlas=181276165 - atlas=181276165&plate=100883818&structure=16382&x=7320.001282354798&y=4255.999940814394&zoom=-4&resolution=16.91&z=5](http://atlas.brain-map.org/atlas?atlas=181276165-atlas=181276165&plate=100883818&structure=16382&x=7320.001282354798&y=4255.999940814394&zoom=-4&resolution=16.91&z=5)