GLIAL RESEARCH IN GERMANY 1995

The cover shows a depthcoded 3D reconstruction of an electron microscopy section series of a Bergmann glial cell process. Bergmann glial cells are radial glial cells in the cerebellum. There cellbodies are located in the Purkinje cell layer and their processes run through the molecular layer and terminate at the pia. A Lucifer Yellow filled cell was converted into electron dense material and 50nm sections were examined with an electron microscope. The digitized data of 100 sections were used to calculate the 3D reconstruction. The depthcoded image (top- bright, bottom-dark) shows the ramnified branches of a large processes (upper left), which ensheat the dendrites of the Purkinje cells. (T. Möller, J. Grosche and H. Kettenmann, unpublished data).

Preface

This is the second issue of a brochure summarizing glial research activities in Germany. The first issue was assembled in March 1993, thus two years ago. We now feel that the rapid development in this challenging field requires an update. The interest in glia research was mirrored in a vivid demand for the first issue from all over Europe and we are hopeful that this brochure is the starting point for a European directory including all glial research groups in Europe.

The introduction of this brochure is based on a proposal submitted to the Deutsche Forschungsgemeinschaft for establishing the present "Schwerpunkt" on "Functions of Glial Cells". The program committee consisted of Bernd Hamprecht, Helmut Kettenmann, C. M. Müller, and Jutta Schnitzer.

Most of the contributors to the brochure are members of this "Schwerpunkt". We, however, learned during the assembly of these two brochures that much more groups are focussing on glial research and some of them are included. We hope that this brochure will facillitate cooperations among groups and may be also a nucleus for common projects between partners within Europe.

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Introduction

Research programs world wide have shown in the last decade that glial cells play an important role for the function of the nervous system. The functional capabilities of these cells go far beyond the original concept which regarded glial cells as supportive elements of the nervous system. New research has redefined the role of these cells and determined the following functions:

1. Glial cells play a pivotal role for the development of the central nervous system. They form guiding structures for migrating neurons and interact via cell adhesion molecules. Moreover, they synthesize a number of important neurotrophic factors that appear critical for normal development.

2. Astrocytes and microglial cells - subpopulations of glial cells - play important roles for immune function within the central nervous system (CNS). For example, it has been recently demonstrated that astrocytes can act as antigen-presenting cells and microglial cells, in particular during brain injury or in response to immune-mediated disease, phagocytose and remove cellular debris.

3. Glial cells, in contrast to the classical concept, are not electrically passive, but have a large repertoire of receptors, transport molecules and ion channel. They are equipped, therefore, to influence the electrical acitvity of the CNS in a great variety of ways.

4. Glial cells play many roles for the clinical neurosciences. The disease multiple sclerosis provides a clear example of this. The symptoms are due to degeneration of myelin in the CNS and myelin, of course, is produced by oligodendrocytes. The initiating steps for the destruction of myelin are at present unknown as are the factors which induce the formation of new myelin. The majority of primary brain tumors, including the most lethal varieties, are formed by an uncontrolled growth of glial cells. Thus, an understanding of the factors which control the development of glial cells will be necessary to understand CNS specific diseases and may help to develop strategies for treatment.

It is thus important to carefully consider glial cells for understanding complex brain functions. New methological approaches with cell biological, immunocytochemical, molecular biological, and electrophysiological methods open the possibility to study identified glial cells under defined conditions. Due to these advancements a large number of laboratories have been attracted to glial research. The present "Schwerpunkt" will coordinate German scientists working in this field and it is meant to stimulate further research on this topic. The specific aims of the Schwerpunkt are as follows:

1. Which factors control the development and proliferation of glial cells? How do glial cells influence other brain cells?
2. Are glial cells functionally involved in plasticity of the central nervous system and what role do they play during regeneration?
3. How are glial cells involved in the immune responses of the central nervous system?
4. Are there glial cell specific biochemical pathways in the central nervous system?
5. What is the role of glial cells in the regulation of brain extracellular ions and volume?.
6. Are glial cells involved in signal transduction in the central nervous system?

State of glial research

The brain is composed of three main classes of cells: neurons, endothelial cells and glial cells. Glial cells outnumber neurons ten to one and represent about half of the volume of the brain. In contrast to these facts, CNS research has mainly concentrated on neurons. Thus, glial cells have been

largely ignored in most investigations about the brain's functions. Entire areas of neurobiological research, such as the study of neuronal networks, disregarded glial cells altogether.

With the discovery of glial cells, Rudolf Virchow believed that they formed a kind of brain connective tissue and represented the passive matrix in which neurons were embedded. At present, we know that glial cells are metabolically highly active and fulfill a number of functions for the developing and adult central nervous system. We now know that glial cells participate in all of the brain's major functions although the details of this participation are, in most instances, unclear.

Three main classes of glial cells have been described in the CNS: astrocytes, oligodentdrocytes and microglial cells. Astrocytes are thought to play an important role in the homeostasis of the extracellular environment with regard to ions, transmitters and products of metabolisms. Oligodendrocytes in the CNS, and Schwann cells in the peripheral neuron system, insulate axons of nerve cells by formation of leave myelin sheath. Mircoglial cells have a functional importance for the immune system of the CNS. The subsequent summary of the present state of research on functions of glial cells will deal with each of these three cellular groups. It has, however, become evident that there are many interactions between these glial cell subtypes. This is particularly important for the differentiation of glial cells, for the formation of myelin and in regard to immunological processes. Moreover, there are multiple important interactions between neurons and glial cells, and the number of these is most likely far beyond our present understanding.

The present knowledge on glial cells makes it evident that the action and reaction spectrum of glial cells goes far beyond the original concept of a passive matrix in the central nervous system. Glial cells are involved in the development of the CNS and for the normal functioning of the brain, including its interaction with the immune system. Furthermore, it is becoming evident, that these cells fulfill their tasks by interaction among each other and with other brain cells. Glial cells are therefore an important part of the brain and must be taken into consideration to explain brain functions. In addition, disturbances of glial function may importantly be related to neurological diseases. Thus, the clarification of these mechanisms is an important step to understand the brain.

Aims of the Schwerpunkt program

The aim of the Schwerpunkt program is to discover the importance of glial cells for the function of the CNS. In detail, we would like to answer the following specific questions:

1. Which glial cells are involved during the developement of the nervous system?
These projects address the questions of how glial cells develop from precursor cells and how their properties change during these developmental stages. Glial cells can be identified at different developmental stages using cell type specific and developmental or stage specific antibodies. In this context the question will be studied whether glial cells are different in different areas of the brain. Moreover, the search for new markers to find a pattern of the glial cell development should be possible. In this context, functionally important molecules may play a key role like for instance proteins which are involved in the formation of myelin. By transfection with oncogenes it should be possible to freeze glial cells in defined developmental stages. With proper transfection, differentiation could be controlled by external stimuli such as heat shock. Of particular interest are the early developmental forms of glial cells which are not as well characterized. These precursors play key roles for regeneration since they are still proliferative and have a large plastic capability. These cells may play key roles in understanding regeneration.

- Which factors control the development and proliferation of glial cells?
We would like to ask the question which factors control proliferation and differentiation of glial cells. These control factors could either be substances such as the well-know epidermal growth factor or components of extracellular matrix and cell membranes (like laminin). These factors need

to be characterized with respect to their function and molecular structure. This directly leads to the question of which cells produce factors and what regulates their production. This implies that a number of regulating circuits may interact where a number of different cell types are involved. This basic research is also of clinical importance since most brain tumors of the CNS where the control of proliferation and differentiation is disturbed are of glial origin.

- Do glial cells influence the behavior of other cells?
As glial cells are influenced with respect to proliferation and differentiation by their environment they in turn can also influence other cells. Most often the partner for such an interaction is a neuron and many previous studies have concentrated on neuron-glia-interaction. It is known that glial cells release soluble factors which control differentiation and survival of neurons. Moreover, glial cells participate in the production of the extracellular matrix which can influence the growth of neurons. A further focus of the interest are contact related interactions such as mediated by cell adhesion molecules which are not only important for cell recognition but can also cause changes in the physiological properties of the interacting cells. In addition to interactions of neurons, astrocytes interact with endothelial cell. It is speculated that this interaction induces the tight junctions between the endothelial cells forming the blood-brain barrier. This structure controls the exchange of substances between blood and brain and guarantees the CNS cells an isolated environment.

2. Are glial cells involved in the regeneration of neuronal connections?
In a number of projects the role of glial cells during the regeneration of the nervous system will be analysed. The ability of the CNS to regenerate after injury is important to understand the states of many CNS deseases such as multiples sclerosis or spinal cord injury. Glial cells play a pivotal role for the regeneration of white matter tracts. It is of general knowledge that after injury white matter tracts in the central nervous system fail to regenerate in contrast to the peripheral neuron systems where axon tracts may regenerate after injury. While this is true for mammals, with fishs and amphibiens such regeneration is even possible in the adult. In the meantime we have learned that the surface of oligodendrocytes in the mammalian CNS contains non-permissive structures which prevent regeneration of neuronal processes. In addition, differentiated CNS glial cells of mammals miss permissive molecules which have expressed in the periphery by Schwann cells enabling regeneration. It will be studied how oligodendrocytes differ in mammals and fish, why fish oligodendrocytes are growth permissive, i.e. they do not only prevent neuronal regeneration. In addition, the permissive properties of the myelinating glial cells of the peripheral nervous system, the Schwann cells, will also be studied. A further aspect deals with the influence of the vascularisation after damage. Interaction of glial cells with endothelial cells also controlling regenerative processes will be studied.

- Which factors control the formation of myelin?
The myelination of vertebrate axons permits saltatory conduction and thus rapid signal transfer. Myelin is produced in the CNS by oligodendrocytes, and in the periphery by Schwann cells. Some of the groups address the question of which factors control the formation of myelin during development. These factors can be either cell site contacts or mediated by soluble substances. This research will be important to understand multiple sclerosis.

- Are glial cells involved in plasticity?
The neuronal plasticity is the basis for the formation of connections during development and for learning and memory in the adult brain. CNS plasticity is mainly explained on the basis of synaptic contacts. It is, however, known that glial cells closely interact with synapses. A number of new studies imply that glial cells and in particular astrocytes may be involved in CNS plasticity. The mechanisms involved are so far entirely speculative. Some of the groups will study such mechanisms in the hope of revealing the molecular interactions between neurons and glial cells that control plasticity.

3. What is the role of glial cells in CNS immune response?

In recent years we have learned that glial cells are involved in immune functions of the central nervous system. It has become evident in the last years that cells of the immune system such as activated lymphocytes can pass into the brain tissue and interact with glial cells in a complex manner. Two aspects of these interactions have become important:

1. One interaction is mediated by soluble substances. Lymphocytes can activate glial cells via interleukins. In return, glial cells release substances which can modulate the response of immune cells.
2. Presentation of antigene by glial cells
   After induction of MHC antigens (for instance by interferon gamma) astrocytes and microglial cells (but not oligodendrocytes and neurons) present protein antigens on the surface in conjunction with the major histocompatibility complex; this can be recognized by T-cell receptors. This research will be a basis for the understanding of physiological autoimmunity which is important for understanding inflammatory diseases.

- Are there glial cell specific pathways in the CNS?

The recently postulated functions of glial cells are the support of neurons and the removal of components from the extracellular space such as neurotransmitters. To fulfill this task, glial cells must express a defined repertoire of enzymes and transport molecules. Some of the projects address the question whether glial cells express specific enzyme and transport molecules which are optimised for that task. Examples are

1. uptake systems for glutamate, taurine as a potential osmoregulator, creatine for energy storage
2. detailed investigation of carboanhydrase (for pH and volume regulation) particularly in oligodendrocytes
3. enzymes of metabolic pathways such as for the genesis of glucose. In return, one can also ask the question which enzymes are specificly expressed by glial cells. This, in return, may give answers to new functions of glial cells.

- How do glial cells control extracellular ion and volume homoestasis - importance for epilepsy and brain damage?

Kuffler and colleagues recognized that glial cells control the extracellular potassium concentration. During neuronal activity potassium rises in the extracellular space and glial cells modulate these peak increases. Disturbances in these glial functions could lead to excess potassium accumulation and may induce epilepsy or spreading depression. The transport systems of glial cells have not yet been studied in complex systems. Such an example would be brain slices of the hippocampus which is a very established model for epilepsy research. New research has indicated that neuronal activity does not only affect the extracellular potassium concentration, but has also profound impact on the intracellular pH, chloride concentration or the volume of the extracellular space. It has become therefore increasingly important to understand the transport systems for pH and chloride, and, in particular, the factors which regulate the activity of these systems. These knowledges will also be the basis to understand the changes in volume which are induced by neuronal activity. A number of transport systems are involved, and some groups focus on the properties, control mechanisms and the expression of these transport systems in the various types of glial cells. Such volume regulation is of large clinical importance since brain damage leads to the swelling of astrocytes. This swelling is the cause for most casualities after brain damage. Therapeutical approaches can only be developed if the basic mechanisms of the glial ion and volume regulation is understood.

- Are glial cells involved in the signal transduction of the CNS?

Glial cells express a variety of receptors for neurotransmitters and neurohormones. This implies that the cells may sense neuronal synapse mediated activity. From there, four lines of reseach have been developed:

1. Does the activation of glial receptors lead to a change in gene expression or proliferation of glial cells? In return, these modulated glial cells could again influence neurons.

2. Most of the glial receptors have been characterized in cultured glial cells. It is therefore an important question whether these receptors are expressed in the intact CNS and if there are differences among the glial cell types and among the brain regions.
3. Which second messenger pathways are coupled to glia receptors?
4. Activation of receptors can lead to waves of calcium which can spread in glial environment. This signal has been implied to complement the neuronal activity.

Functions of Astrocytes

The glial cells originally described by Virchow were most likely astrocytes. Based on studies of cell lineage, two types of astrocytes have been distinguished. Morphological studies show even further diversity of this cell group. Beside the classical star shaped astrocytes, radial glial cells with long processes have been described such as Bergmann glia, tanycytes, Müller cells, and pituicytes. One of the important functions of astrocytes was discovered in the sixties by Kuffler and coworkers, namely the regulation of extracellular potassium concentration. This becomes important since neurons release potassium into the extracellular space during activity. Due to their membrane properties intensive electrical coupling, astrocytes can redistribute extracellular potassium. In the meantime, more functions on the regulations of the homeostasis of the extracellular space have been described. These cells regulate extracellular pH and extracellular volume regulation, and remove and metabolize neurohormones and neurotransmitters. To fulfill this task, these cells have active transport mechanisms specific for hormones and transmitters. Astrocytes can also produce hormones such as nerve growth factor, interleukin-1, insulin-like growth factor I. In particular, the radial glial cells form the guiding structures for neuronal migration. There is even recent evidence that glial cells can play an important role for the establishment of neuronal connections.
A number of receptors for extracellular proteins, hormons, neurotransmitters and petides have been recently discovered on astrocytes. Activation of these receptors influence astrocytic ion channels and intrecellular second messenger pathways. The functional importance of these receptors for CNS function has not yet been described in detail, but their presence suggests a contribution of neuron-glia-interaction.

Functions of microglial cells

Microglial cells play an important role for immunological processes in the CNS. This is not an isolated function of the cells but comes about due to close interaction with other glial cells such as astrocytes. For a long time, the central nervous system was thought to be an immunologically privileged part of the body which was not accessible to circulating lymphocytes, cells which are important for immune functions. Research on cellular autoimmune reactions which are important for the pathology of multiple sclerosis (MS) has changed this concept. Moreover, microglial cells have the property to phagocytose damaged cells, either during brain injury or during development. Only during these activated phases microglial cells express the MHC II antigens.
Experiments in cell cultures have improved our knowledge on the interactions between the nervous system and the immune system. Activated T-lymphocytes produce and release interferon which leads to the production and expression of MHC II from the cell surface of astrocytes. It is so far unknown whether interferon has an influence on microglial cells; astrocytes and mircroglial cell produce and release interleukin-1 thereby activating T-lymphocytes. This increase of interleukin-1 promotes the proliferation of astrocytes leading to important questions on the involvement of microglial cells during development. It is also likely that they are involved in angiogenesis by secretion of tumor necrosis factor.
These findings imply that a study of microglial cells has opened a new field to understand the interaction of the immune and nervous system.

Functions of oligodendrocytes and Schwann cells

The classical function of oligodendrocytes and Schwannn cells is the formation of myelin which permits the saltatory conduction of axons. The importance of this function becomes evident if myelin is destroyed, for instance in multiple sclerosis. Similar symptoms can be observed in different mouse mutants which have defect in the formation of myelin. These defects are due to the lack of oligodendrocyte of Schwann cell specific molecules. Transplantation of oligodendrocytes or their precursors in animal models could induce remyelination. Oligodendrocytes play an important role for the control of regenerative processes in higher vertebrates. Recent studies reveal that these glial cells express molecules which prevent regeneration. Schwann cells, in contrast, lack these molecules enabling regeneration in the peripheral nervous system. Moreover, these cells release growth promoting substances such as nerve growth factor.

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Dr. Karl Bauer MPI für experimentelle Endokrinologie Feodor-Lymen-Str. 7 30625 Hannover	Metabolism of carnosine and inactivation of neuropeptides by glial cells
Dr. Gert Brückner Paul-Flechsig-Institut Universität Leipzig Jahnallee 59 D-04109 Leipzig	Cytochemistry of glia and extracellular matrix
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Prof. Dr. Rolf Dermietzel Medizinische Fakultät Universität Regensburg Universitätstr. 31 93053 Regensburg	Structural and functional identity of glial gap junctions
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Dr. Manuel Graeber Institut für Neuropathologie Universität München Thalkirchnerstr. 36 80337 München	Glial cells as sensors of tissue pathology in the human brain: genotype-phenotype in neurodegenerative disorders Microglia in the normal and diseased human brain
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Prof. Dr. Georg W. Kreutzberg Neuromorphologie MPI für Psychiatrie Am Klopferspitz 18 A 82152 Martinsried	The role of microglial cells - Microglia activation
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Dr. Jutta Schnitzer Zelluläre Neurowissenschaften Max-Delbrück-Centrum für Mol. Medizin Robert-Rössle-Str. 10 13122 Berlin-Buch	Properties of glial cells in the developing and mature vertebrate nervous system
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Dr. Christian Steinhäuser Institut für Physiologie Friedrich-Schiller-Universität Teichgraben 8 07743 Jena	Voltage- and ligand-operated ion channels of central glial cells
Prof. Dr. Stoffel Institut für Biochemie Medizinische Fakultät Joseph-Stelzmann-Str. 52 50937 Köln 41	Myelin structure - Myelination as developmental process - Dysmyelinoses - Glial Glutamate Transporters - Human disease models in the mouse by gene targeting
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Structure of the Group Grant ("Schwerpunkt") "Functions of Glial Cells

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General Research Interests

Capabilities of Mature Oligodendrocytes and Astrocytes

Oligodendrocytes (OL) are the cells in the CNS which manufacture and maintain the myelin sheath. Two major line of research interests were followed after culturing and characterisation of OL were possible: a) to study the capabilities of mature OL and b) to investigate the differentiation steps within the glial lineage. Mature OL were previously considered as lazy cells, which have more or less fulfilled their tasks. Recent culture and in vivo studies, however, have shown that mature OL can undergo plasticity and are integrated in the neural orchestra as an active member. We have isolated and cultured OL and astrocytes from the adult pig brain. We have shown that OL can produce and release PGs, respond to neuroactive substances such as NGF, can undergo proliferation, and are capable to myelinate. In contrast, astrocytes do not respond to NGF similarly to OL.

Research Project on Glial Cell Structure and Function in Health and Disease

Signaltransduction in Oligodendrocytes Experimental De-Remyelination

We have shown that protein kinase C (PKC) activating substances such as phorbol esters induce OL proliferation and process formation. On the search for replacing the phorbol esters surprisingly NGF was found to mimick the TPA effects. The kinetics, however, were different. Low and high affinity NGF receptors were identified. NGF induces the tyrosine phosphorylation of several proteins. Studies on the NGF signal transduction pathway are initiated. They may help us to define the rails which are important for proliferation, process formation, and the production of myelin proteins. Furthermore, in vivo experiments are undertaken to elucidate the role of NGF during de-remyelination. In addition, it is planned to investigate glial progenitor cells isolated from fetal pig brains.

Methods Available

tissue culture techniques
immuno-methods
biochemical methods
antisense-oligo techniques
(in prep)

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5 References

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General Research Interests:

Interactions of glial cells with regnerating CNS neurons

It is still an unresolved problem why adult mammalian CNS neurons, unlike those in fish or amphibia, are unable to regenerate long axons after a lesion. Most of the hypotheses which have been generated in the recent years have focussed on the changes that occur in the different glial cell lineages during development and after lesions. Both, astrocytes and oligodendrocytes impede axon growth after lesions in vivo. To examine the relative influences of characterized glia populations and cell intrinsic determinants selectively, apropriate in vitro models are necessary. We have developed tissue culture techniques which allow studying the interactions of embryonic, regenerating adult rat and fish RGC axons with characterized glia populations.

The aim of our studies at present is to determine the relative contribution of reactive astrocytes and astrogliosis to the inhibition of axon regeneration in the adult CNS as compared to the inhibition by oligodendrocytes. Moreover, we try to identify the molecules that are responsible for the inhibition of axon growth or for the nonpermissiveness of the astrocytes at lesion sites.

Research Project on Glial Cell Structure and Function in Health and Disease:

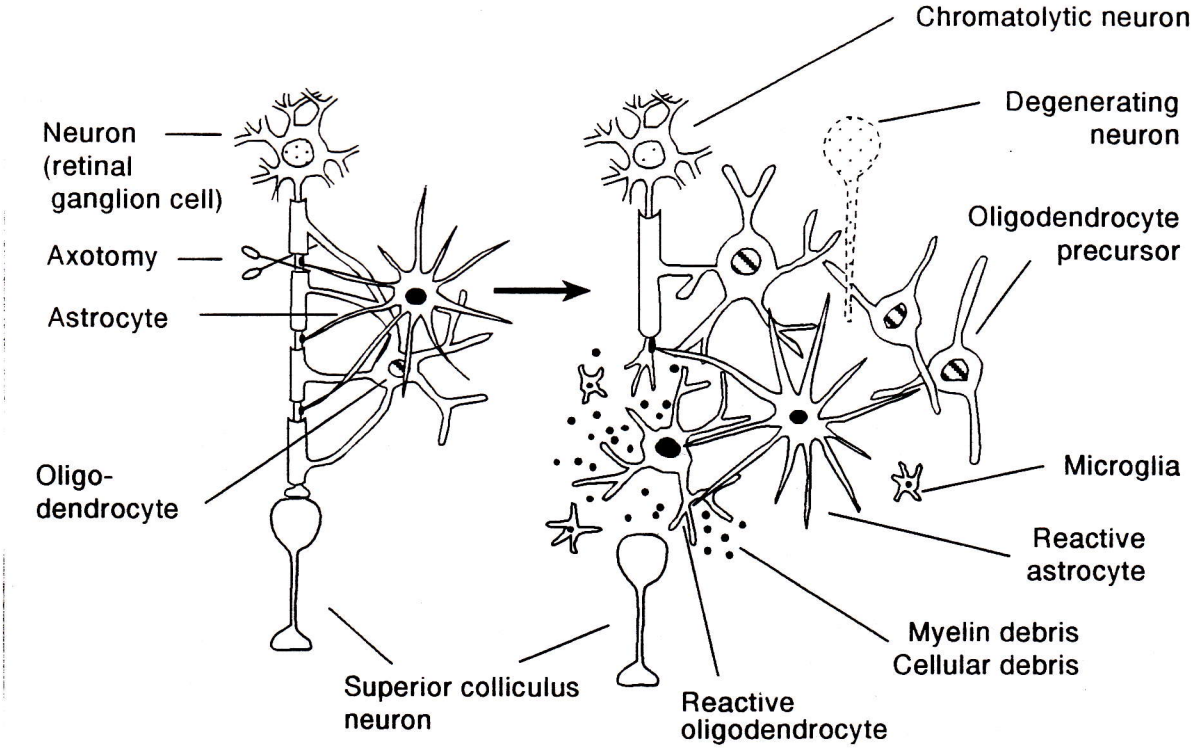
To determine, which types of glial cells are present at lesions sites in vivo, we have studied the glial response to optic nerve axotomy. Glial cells were obtained from normal and crush-axotomized optic nerves. In cultures from axotomized nerves astrocytes, different oligodendrocyte progenitor cells and mature oligodendrocytes were found in large numbers. In contrast, significantly fewer glial cells were present in cultures from normal nerves. Thus, optic nerve injury enhances the ability of different glial populations to survive in vitro. The distinct time window of proliferation of oligodendrocyte progenitor cells which was observed in cultures from axotomized nerves suggests the regulatory influence of blood derived factors which are not present in normal nerves after in vitro axotomy.

The aim of the presnt project is to identify the factors which regulate cell proliferation and transformation of adult rat optic nerve astrocytes and to study the interaction of regenerating retinal ganglion cells with reactive astrocytes in vitro.

Methods Available:

Tissue culture techniques for:
- neonatal and adult rat retinal ganglion cells
- neonatal an adult rat CNS and PNS glial cells
- electron microscopy
- time lapse video-microscopy

Reaction to axotomy in the CNS



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C.Przyrembel and M.Bähr (1993) The reaction of optic nerve glia to axotomy. *Neurosci. lett.* 163: 227-230.

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General Research Interests

Metabolism of carnosine and inactivation of neuropeptides by glial cells.

Carnosine (ß-Ala-His) and structurally related dipeptides (e.g. homo-carnosine, γ-aminobutyryl-histidine, etc.) are well-known constituents of excitable tissues (brain and muscles) but their physiological functions still remain completely enigmatic. While it has been suggested that carnosine might act as a neurotransmitter of the chemoreceptor neurons, our results demonstrate that in the CNS these peptides are synthesized by glial cells. In addition we observe a very rapid uptake of carnosine by glial cells which is mediated by a dipeptide-specific, high-affinity transport system. Our present studies focus on the identification of specific glial cells that are equipped with the transport system (e.g. glial cells of the CNS-olfactory bulk, folliculostellate cells of the pituitary, etc.) and/or the capacity to synthesize these peptides. We are also interested in the degradation of neuropeptides by ectoenzymes located on the surface of glial cells.

Research Project on Glial Cell Structure and Function in Health and Disease

Various cell lines (glioblastomas, astrocytomas) are screened with regard to their capacity to synthesize carnosine and related peptides and with regard to the dipeptide-transport system.

Methods Available

General culture techniques / Radioautographic and fluorescence measurement techniques

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Schulz, M., Hamprecht, B., Kleinkauf, H., Bauer, K. (1987) Peptide Uptake by Astroglia-Rich Brain Cultures. J. Neurochem. **49**, 748-755;

Bauer, K., Carmeliet, P., Schulz, M., Baes, M., Denef, C. (1990) Regulation and Cellular Localization of the Membrane-Bound Thyrotropin-Releasing Hormone-Degrading Enzyme in Primary Cultures of Neuronal, Glial and Adenohypophyseal Cells. Endocrinology, **127**, 1224-1233.

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General Research Interests

Cytochemistry of Glia and Extracellular Matrix

Glial cells structurally adapt to morpho-functional features of neurons. Recent data indicate that the extracellular matrix at the neuron-glia interface may substantially determine the neuronal microenvironment. Glycoconjugates such as proteoglycans seem to play an important role. They are concentrated as polyanionic macromolecules in perineuronal nets, certain neuropil regions and at nodes of Ranvier. Many structural aspects and the exact chemical composition of the matrix complexes are unknown and their functions are still obscure. It is the aim of our studies to analyze the construction of those perineuronal specializations and to characterize the glial components and associated glycoconjugates with respect to the types of ensheathed neurons using cytochemical methods at the light and electron microscopic level. We hope to contribute new data on glia-neuron communication systems mediated by the extracellular matrix. Our studies are performed against the background of brain functions in the adult and developing brain as well as during pathological processes such as Alzheimers disease.

Research Project on Glial Cell Structure and Function in Health and Disease

Cytochemical and Structural Properties of Perineuronal Nets

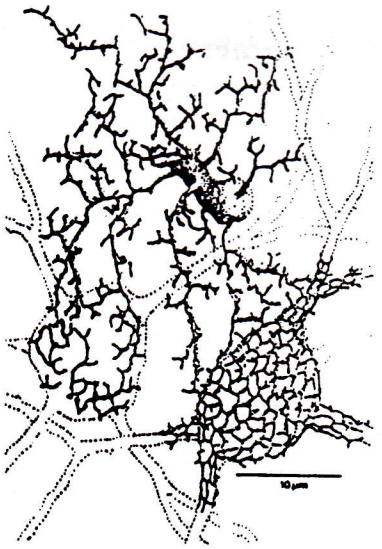
The glial component of perineuronal nets was visualized in the rat brain with the Golgi technique (Brauer et al., J. Hirnforsch. 23: 701, 1982). Similar lattice-like structures in the microenvironment of neurons could be demonstrated using N-acetylgalactosamine (GalNac)-binding lectins and immunocytochemical methods. These extracellular matrix chondroitin sulphate proteoglycans ensheath somata, parts of dendrites and axon initial segments of various types of neurons in more than 100 brain regions. In the neocortex and hippocampus of rats and several other mammals the nets are associated with non-pyramidal cells arranged in patterns which mirror the extension of cortical areas. Dual labelling demonstrated that GalNac-containing nets frequently surrounded neurons characterized by the calcium-binding protein parvalbumin. To investigate the spatial relationship between glial cell processes and glycoconjugates of perineuronal nets, GFAP, S100-protein and glutamine synthetase were detected in dual-label experiments. It was concluded from these investigations that perineuronal nets represent a glia-neuron interface specialized by extracellular proteoglycans .

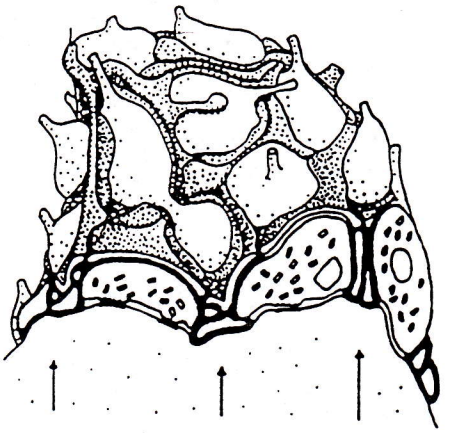
Our future projects will further consider developmental and phylogenetic aspects, but will be focused on activity-dependent variations and pathological changes of the glia-matrix-neuron interface including studies of regulatory factors involved.

Methods Available

Lectin-cytochemistry and immunocytochemical detection of glial and neuronal markers including dual peroxidase and dual- or triple fluorescence techniques

Electron microscopy





Left: Golgi impregnation of a glial cell forming perineuronal nets on non-pyramidal neurons in the rat cerebral cortex (drawing: K. Brauer). Right: Perineuronal net consisting of extracellular matrix glycoconjugates (black) interposed in the glia-neuron-interface as demonstrated in electron microscopic studies.

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General Research Interests

Ionic signals in nerve and glial cells

Nervous systems are neuron-glia systems. The communication between neurons and glial cells via the extracellular spaces is of particular functional importance. In a system of such closely associated cell types, which share a common microenvironment, local signals are likely to be received by both neurons and glial cells, irrespective of its origin. Ionic transients, in particular of Ca^{2+} and H^+, occur intra- and extracellularly, following neuronal stimulation, transmitter and hormone release, or due to the action of neuromodulators, pumps and carriers. Hence, processes of induced ionic shifts and ionic regulation may overlap and merge to characteristic transients, which could be essential steps in the signal cascades for intra- and intercellular communication.

Research Project on Glial Cell Structure and Function in Health and Disease

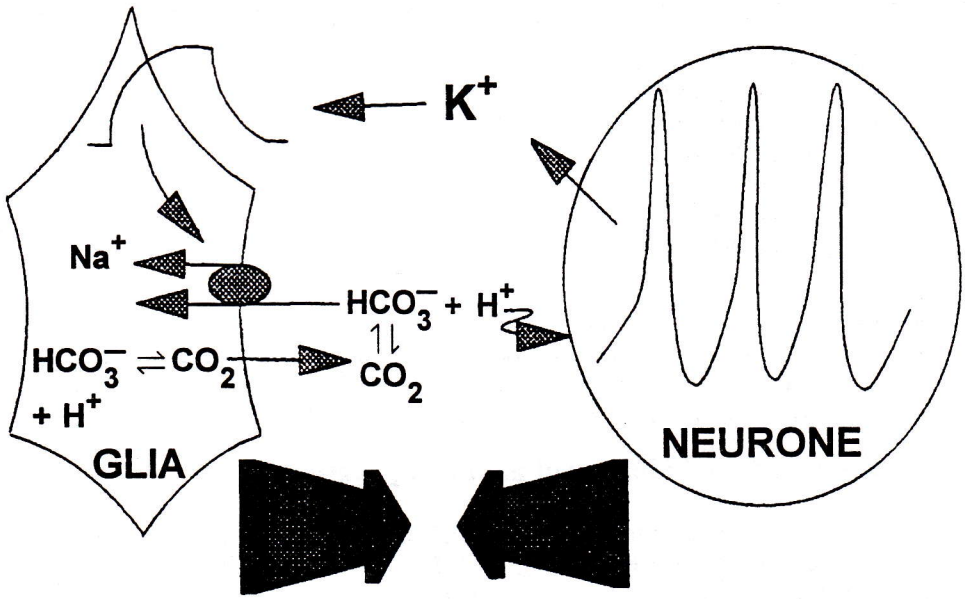
Calcium and pH in glial cells

Ca ions play an important role as charge carrier and second messenger, modulating intracellular enzymes and ion channels. We look at different pathways of Ca^{2+} into identified glial cells and aspects of Ca^{2+} regulation by glial cells. These cells display Ca^{2+}-permeable voltage- and transmitter-activated membrane channels and various intracellular Ca^{2+} stores. We study the mechanisms by which glial cells control their low intracellular Ca^{2+}, how they extrude Ca^{2+}, and whether they are involved in the regulation of the Ca^{2+} level in the extracellular spaces.
Intra- and extracellular pH transients may also have signalling character. We have recorded large and rapid changes of pH in glial cells, neurons and in the extracellular spaces, and study the mechanisms of such pH changes.
We use ion-senstive microelectrodes and fluorescent dyes to monitor the intra- and extracellular ion activities, and electrophysiological techniques to study the mechanisms of ionic fluxes, including regulation, in vertebrate and invertebrate glial cells.

Methods Available

- Measurement of ion activities, notably Ca^{2+} and H^+, using ion-sensitive microelectrodes and fluorescent dyes in single cells and cell cultures
- Patch-clamp techniques in cultured cells, cells in situ or in brain slices
- Conventional electrophysiological and immunocytochemical techniques

Ionic crosstalk between neurones and glial cells



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General Research Interests

Structural and functional identity of glial gap junctions

Gap junctions allow the direct intercellular exchange of ions and low molecular weight metabolites, including second messengers, between adjacent cells. By this mode of communication signal molecules are directly transferred without leakage into the extracellular space. Glial cells, especially astrocytes, are furnished with an extensively elaborated complement of gap junctions. Thus the degree of coupling between this glial species is regarded to be high. Functional communication between glial cells in form of Ca2+ osszilations and IP3 movement has been shown to be mediated via gap junctions. Insofar gap junction provide the structural backbone by which glial cells are assembled in form of a functional syncytium.

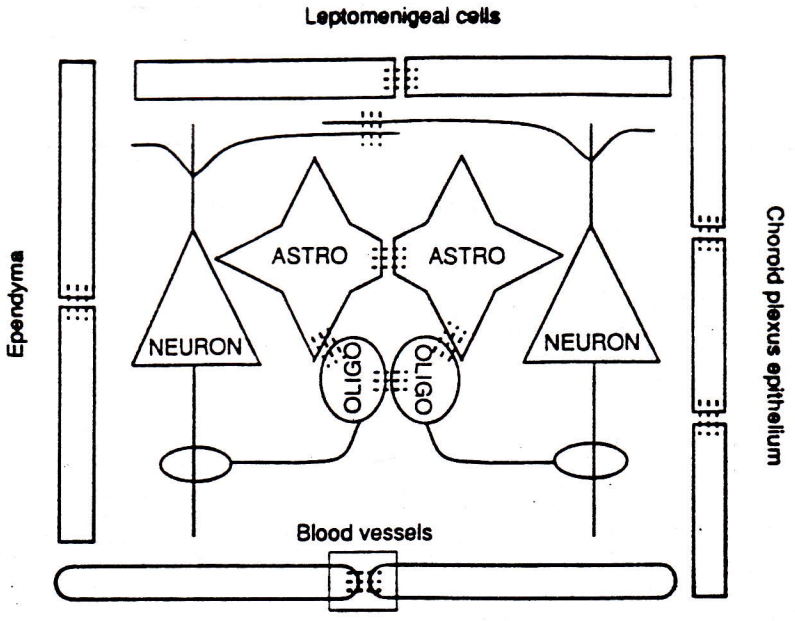
Research Project on Glial Cell Structure and Function in Health and Disease

Molecular identity and plasticity of interglial gap junction communication

Connexins are the channel-forming proteins of gap junctions. Diverse isoforms are expressed in different tissues. Astrocytes and oligodendrocytes display a diversity in connexin expression. While connexin43, originally cloned from heart tissue, is highly expressed in astrocytes, oligodendrocytes express connexin32. Both connexins, however, provide different functional properties, i.e. voltage dependence, pH sensitivity. One of our present projects is to elucidate whether heterologous coupling between both types of makroglial cells is feasible and to characterize the functional properties of such chimeric junctions. Accumulating evidences also indicate that the strength of coupling between glial cells shows a high degree of plasticity according to the actual functional requirements of the brain tissue. A further goal of our project is to define the cell biological aspects which prove responsible for the plasticity of interglial communication.

Methods Available

Isolation of gap junction proteins
Molecular biological techniques
Microinjections of dy tracers
Light and electron microscopical immunolabelling
Tissue culture techniques



Gap junctions between communicating cells in the central nervous system. Within most cell populations, gap junctions form the primary route of signal transmission. For neurons, gap junctions coexist with chemical synaptic transmission. Each compartment as drawn represents the aggregate of subcompartments with variable requirements for direct intercellular communication.

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General Research Interests

Humoral glial-neuronal interactions

Neurotrophic factors play a crucial role in neuronal development, maintenance, and regeneration. While it is has been generally assumed that neurotrophic factors are specifically provided by the target tissue of a given neuronal cell type, our studies and those of others have demonstrated that growth factors also indirectly affect neurons through glial-mediated processes. Specifically, we observed that a number of identified growth factors primarily affect glial cells which in return influence neuronal survival and differentiation by a yet unknown humoral mechanism. The aim of our present studies is to further characterize these humoral glial-neuronal interactions. These studies may not only provide new insights into the role of growth factors during brain development but may also help to understand the mechanisms underlying certain neurodegenerative diseases e.g. Parkinson's disease.

Research Project on Glial Cell Structure and Function in Health and Disease

Identification of glial-derived neurotrophic factors for mesencephalic dopaminergic neurons

Our previous studies have demonstrated that mesencephalic glia secrete factors that support dopaminergic cell survival and differentiation. We have recently been able to identify one of these factors as sulphated glycoprotein-2 (SGP-2), a heterodimeric peptide originally isolated from Sertoli cells of the testis. Moreover, we obtained evidence that the neurotrophic activity of SGP-2 on dopaminergic neurons depends on the presence of an additional, as yet unknown, glial factor. Experiments aiming at the identification of the responsible cofactor are presently in progress. Future studies will address the mechanism of this peptide interaction as well as its role in the biological activity of SGP-2.

Methods Available

Cell culture techniques for neurons and glia
Evaluation of growth factor effects on neurons and glia
Biochemical purification of growth factors

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Engele, J., D. Schubert, and M. C. Bohn. Conditioned media derived from glial cell lines promote survival and differentiation of dopaminergic neurons in vitro: Role of mesencephalic glia. J. Neurosci. Res. 30, 359-371, 1991.

Engele, J. and M. C. Bohn. The neurotrophic effects of fibroblast growth factors on dopaminergic neurons in vitro are mediated by mesencephalic glia. J. Neurosci. 11: 3070-3078, 1991.

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Engele, J. and M. Lehner. Regulation of glial-derived dopaminergic growth factors by glucocorticoids and protein kinase C. Submitted.

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Engele, J. Changing responsiveness of developing dopaminergic neurons for extracellular growth factors. Submitted.

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General Research Interests

Glial Recognition Molecules in Neural Pattern Formation

Astrocytes play an important role in forming neural tissues, for example by guiding migrating neurons and growth cones to their destination or by forming transient tissue boundaries designed to segregate neuronal assemblies. We are attempting to identify glial molecules which might mediate these morphogenetic functions. In this context, we study in more detail tenascin glycoproteins and the recently discovered chondroitin sulfate proteoglycan DSD-1-PG. Tenascin glycoproteins are transiently expressed by astrocytes during CNS development and delineate functional processing units in some areas, e.g. the somatosensory barrel field. The generation of a library of monoclonal antibodies and the design of in vitro bioassays served to uncover at least four functional properties of tenascin glycoproteins, namely neuron-binding, the control of neuron migration and of neurite outgrowth, and the repulsion of neurons and of their processes. Current investigations aim at the structural characterization of these functional domains and at the identification of complementary neural receptors. Particular emphasis will be devoted to the elucidation of the repulsive effects of the molecule. Interestingly, the glial proteoglycan DSD-1-PG influences neuronal differentiation and might also contribute to glial functions.

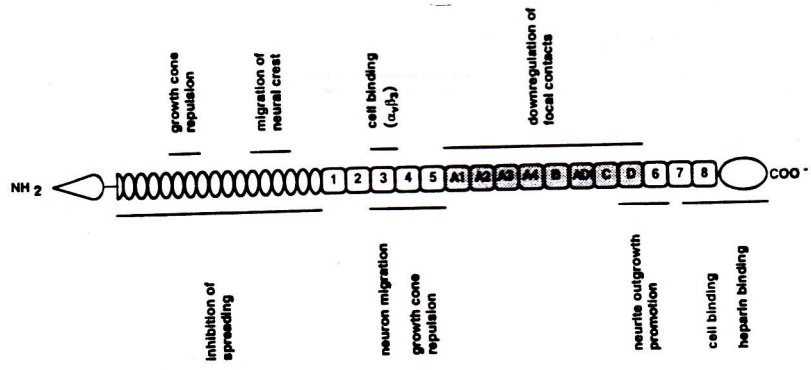
Research Project on Glial Cell Structure and Function in Health and Disease

Glial Extracellular Matrix in Neural Plasticity and Regeneration

It is clear that glial cells are involved in the response of neural tissues to lesion. The mechanisms through which glia affects neuronal behaviour in this context have only partially been elucidated. Interestingly, tenascin glycoproteins are up-regulated under various pathological conditions; thus, tenascin in strongly expressed by Schwann cells upon damage of the peripheral nerve. In the CNS tenascin shows enhanced expression in reactive astrocytes and astroglial tumours. Likewise, the chondroitin sulfate proteoglycan DSD-1-PG is detectable at elevated levels, presumably in reactive astrocytes after CNS lesion. These observations open the possibility, that both glycoproteins and proteoglycans of the extracellular matrix mediate glial influences on neuronal response to CNS pathology. This possibility will be explored by expression studies on pathological specimen of human origin and by investigation of the functional properties of extracellular matrix components in reductionist bioassays. For example, the monoclonal antibody 473HD was used to purify DSD-1-PG from postnatal neural mouse tissues. It could be shown that the proteoglycan promotes neurite outgrowth from embryonic day 18 hippocampal neurons and that this effect involves the binding site of monoclonal antibody 473HD, a specialised glycosaminoglycan structure. The potential implications of this result for the control of sprouting phenomena in lesion areas are currently being investigated. Also, the structure-function analysis of DSD-1-PG will be advanced and refined by molecular cloning of the proteoglycan core.

Methods Available

Primary culture of defined neural cell types
In vitro bioassays for determination of cell adhesion, cell repulsion and neurite outgrowth
Generation of monoclonal antibodies to neural ECM molecules
Purification and biochemical characterisation of neural ECM components and complementary receptors
Molecular cloning of neural ECM components, expression of fusion proteins, in situ hybridisation



Localisation of functional domains of tenascin.

The figure summarises the current view of structure-function interrelationships of tenascin glycoproteins. The functional domains are tentatively projected onto a large isoform. The attributions of functional properties are based on the application of monoclonal antibodies with known binding sites in perturbation assays and of proteolytic fragments or recombinant proteins in in vitro bioassays. Ellipsoid structures indicate EGF-repeats, boxes signify FN3-repeats and a circle at the carboxyterminus designates a fibrinogen-like domain. Alternatively spliced FN3-repeats are shaded.

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General Research Interests

Development and Regeneration of Neuronal Projections

We use the septohippocampal projection in the rat as a model to study the factors underlying the formation of central pathways. Since this projection can easily be transected, it may also be used as a model to study degenerative and regenerative processes of central neurons. This includes studies on the role of trophic factors during development of the septohippocampal projection and after axotomy. Glial cells may play a crucial role in the development of the septohippocampal projection as well as in degenerative and regenerative processes following transection of this pathway in the adult animal. We recently succeeded in establishing the septohippocampal projection in vitro by using slice cultures of septum and hippocampus. Some of the factors underlying the normal development of this pathway, its degeneration and regeneration following axotomy may be better analyzed in this in vitro system.

Research Project on Glial Cell Structure and Function in Health and Disease

At present there is no project of this research group in the DFG Schwerpunkt. However, it can be seen from our general research interests that we are very interested in the role of glial cells during development and regeneration. Thus, we have plans to submit a proposal in the near future.

Methods Available

Histological techniques and tracing techniques for the study of interneuronal connections
Correlated light and electron microscopic immunocytochemistry
Slice cultures
Intracellular labeling of neurons and glial cells in fixed slices
In situ hybridization, PCR technique

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General Research Interests

Glial cells as sensors of tissue pathology in the human brain: Genotype-phenotype correlations in neurodegenerative disorders

An understanding of tissue reactions in nervous system diseases requires the elucidation of glial reactions. With new and sensitive markers of glial activation available, even subtle changes can be detected. This is of great interest to neuropathology as glial reactiveness may serve as an indicator of disease severity. For instance, in neurodegenerative disorders the degree of glial activation may be related to the extent of neuronal cell death. Genetic factors are increasingly ascribed a role in the etiology of Parkinson's and Alzheimer's disease. We have established protocols that allow one to use formalin-fixed and paraffin-embedded brain tissue for molecular genetic studies. Employing histologically verified cases, we perform genotyping at candidate "susceptibility" loci. This includes genomic sequencing of mitochondrial complex I genes (Parkinson's disease) and the determination of ApoE alleles (Alzheimer's disease). Reactions of astrocytes and especially microglia play an important role in the evaluation of histological phenotypes. The aim of these studies is to determine the relationship between histological disease subtypes and specific genotypes.

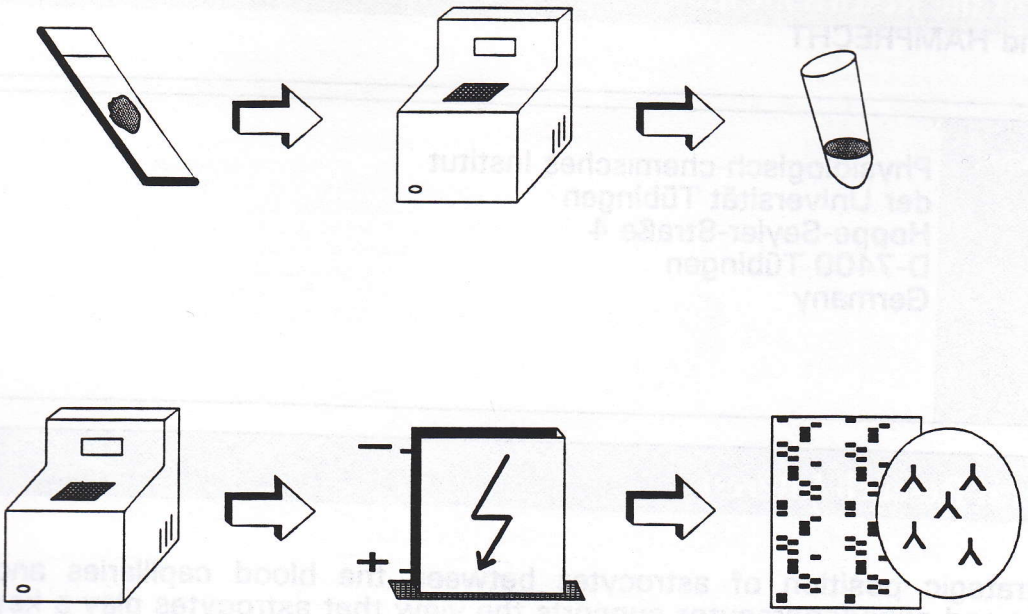
Research Project on Glial Cell Structure and Function in Health and Disease

Microglia in the normal and diseased human brain

In order to learn more about conditions of microglial activation in the human brain, studies on the malleability of microglial phenotype have been started. Microglial expression of immunomolecules such as MHC class II antigens as well as macrophage markers are studied during brain development, in acute and chronic-progressive inflammatory conditions, and in brain tumors. Our developmental study focusses on Rio-Hortega's *microglial fountains*. The aim of this study is to define the ontogenetic relationship between perivascular macrophages and microglia in human brain. *Microglial rod cells* (Nissl's "Stäbchenzellen") are studied in chronic inflammatory diseases that may result in dementia. We are interested in the question whether microglia may be involved in "synaptic stripping" of cortical and hippocampal neurons. Studies of microglia in CNS neoplasms may help to clarify whether microglia could play a beneficial role in the immune defense against brain tumors. In this study, parameters of microglial activation are compared with proliferation and apoptosis/necrosis indices of glioma cells.

Methods Available

Light and electron microscopic immunocytochemistry,
DNA extraction from neuropathological material,
Polymerase chain reaction (PCR),
Restriction enzyme assays,
Non-radioactive direct sequencing of PCR products



A technique for direct, non-radioactive sequencing of PCR products is schematically illustrated (Kösel and Graeber, 1993). Using DNA isolated from tissue specimen of histologically verified brain diseases, genotype-phenotype correlations can be performed at the histological level.

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General Research Interests

The strategic position of astrocytes between the blood capillaries and the neurons and oligodendrocytes supports the view that astrocytes play a key role in the energy metabolism of the brain. Thus, we are testing our hypothesis that one function of these cells is as processing plants for the generation from various compounds such as carbohydrates, amino acids, proteins and fatty acids nitrogen-free molecules that can be used by other brain cells (neurons, oligodendrocytes) as combustible fuel material. To that end methods of enzymology, immunochemistry, cell culture and histochemistry are used to test for the presence of such functions in astroglial cultures and the brain.

Research Project on Glial Cell Structure and Function in Health and Disease

In the past we have shown that in brain the glycogen degrading enzyme glycogen phosphorylase is present in astrocytes, ependymal cells and sensory neurons. Of the 3 isozymes likely to occur in brain it is to be assessed whether or not each of them is associated with one cell type. The cellular location of glycogen synthase will be compared with that of phosphorylase. In astroglial cultures glyconeogenesis from various substrates has been established and its regulation will be investigated. An effort is being made to localize in brain the three key gluconeogenic enzymes and their mRNAy by immunocytochemical and in situ hybridisation techniques. The generation of fuel material from amino acids will be studied by using the ketogenic amino acid leucine. Since for several amino acids the processing to fuel molecules will require the presence of the key enzymes malic enzyme and AMP deaminase, the cellular distribution in brain of the cytosolic and mitochondrial forms of malic enzyme and of the isozymes of AMP deaminase will be analyzed.

Methods Available

Isolation and characterization of proteins - Enzymological techniques - isolation and characterisation of small amounts of metabolites - Generation and characterization of mono- and polyclonal antibodies - Immunocyto - and histochemistry - in situ hybridisation of mRNAs - Cell culture techniques (primary cultures, cell lines) - Studies of transport and metabolism in cultured cells.

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General Research Interests

Ontogenesis and Functional Properties of Radial Glial Cells

Radial glial cells form the principal guiding system for neuronal migration during CNS development. In mammals, these cells are only transiently present during ontogenesis and exhibit impressive capabilities in establishing a continuously enlarging highly ordered scaffold within the rapidly growing brain anlage. During the past years, we have provided evidence for an epigenetic control of their differentiation and alignment exerted by meningeal fibroblasts in vivo and in vitro.

Similar to the factors controlling the ordered establishment and eventual reduction of the radial glial cell system, the principal mechanisms of action of these cells, i.e. the regulated adhesive interaction with migrating neurons are largely unknown. Here, the neuropathology of the "reeler" mutation in mice, a single gene defect dramatically interfering with neuronal migration in the entire CNS, but without any known extraneuronal defects, points to the existence of one adhesion mechanism of an unique significance. The reeler gene as well as its product are still unknown, but indirect evidence has been published that its action may reside in the control of activity of an ectoenzyme, ß(1,4)galactosyltransferase. In a number of non-neuronal systems, this enzyme has been described to function as a cell adhesion factor due to a lectin - like interaction with GlcNAc residues (its acceptor substratum) on e.g. glycoproteins like laminin or uvomorulin. Thereby, the expression of this enzyme seems to be regulated in space and time by a number of different genes, e.g. the T/t - locus operative during morula compaction.

Research Project on Glial Cell Structure and Function in Health and Disease

In-Vitro Differentiation of Radial Glial Cells

Undifferentiated radial glial cell progenitors from the cerebellar external granular layer and cerebral astrocyte cultures are subjected to coculture experiments with meningeal cells or fibroblasts of other origin, e.g. corneal stroma as well as with their conditioned media. Under these conditions, development of fascicles of glial cells with elongated bipolar somata is observed, that are able to guide neuronal migration in vitro. These cells are currently characterized for the expression of CAM patterns and radial glia cell - specific epitopes. Preliminary evidence points to the existence of a subpopulation of glial cells in standard astrocyte cultures from postnatal mouse brain that are able to reexpress radial glial cell markers and morphology (features that are normally lost during early primary culture) upon "mesenchymal" stimuli.

ß(1,4) - Galactosyltransferase as an Adhesion Molecule for Glia - guided Migration

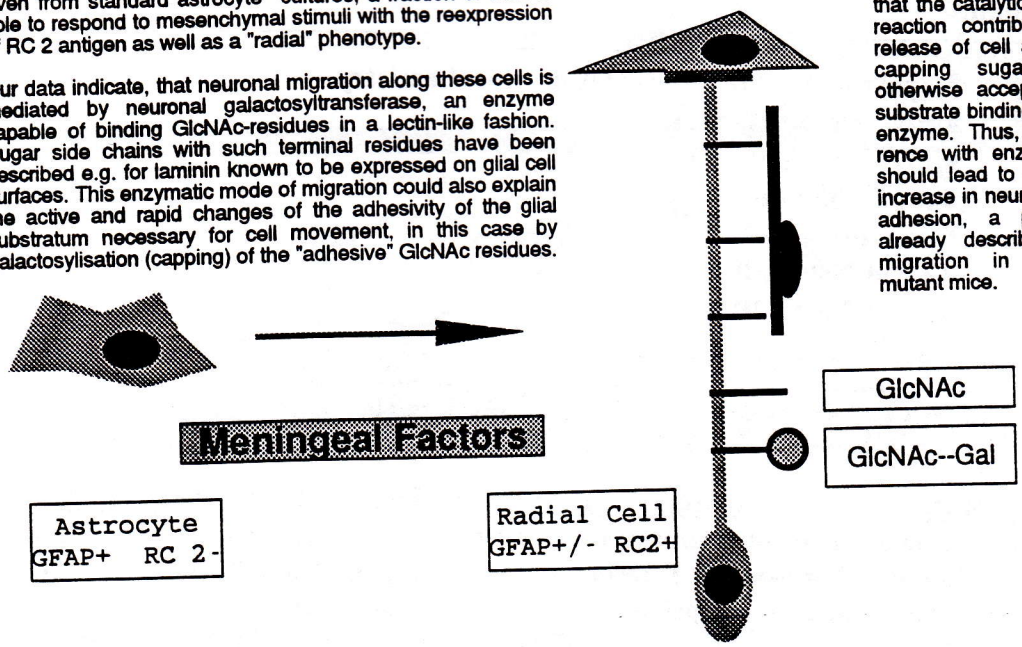
Using antibodies produced in our laboratory, we have localized this molecule to the cell surface of migrating neurons in cell culture; the glial ligand of which is still unknown, but could possibly be laminin. Experimental alteration of enzyme function interferes with neuronal migration along glial fibers in vitro as visualized by time lapse cinematography. In vivo, cell surfaces are immunopositive for the enzyme predominantly in the ventricular and intermediate zones, whereas only subpopulations are stained in the mature brain. The exact developmental expression pattern of this molecule throughout the embryonic body is currently under investigation by immunohistochemistry and in-situ hybridization.

Methods Available

Cell Culture of Dissociated and Organotypic Tissue preparations
In-Vitro Time - Lapse Cinematography
Immunohistochemistry and In-Situ Hybridization
Image Analysis and Morphometry

Even from standard astrocyte cultures, a fraction of cells is able to respond to mesenchymal stimuli with the reexpression of RC 2 antigen as well as a "radial" phenotype.

Our data indicate, that neuronal migration along these cells is mediated by neuronal galactosyltransferase, an enzyme capable of binding GlcNAc-residues in a lectin-like fashion. Sugar side chains with such terminal residues have been described e.g. for laminin known to be expressed on glial cell surfaces. This enzymatic mode of migration could also explain the active and rapid changes of the adhesivity of the glial substratum necessary for cell movement, in this case by galactosylisation (capping) of the "adhesive" GlcNAc residues.



This model would predict that the catalytic step in this reaction contributes to the release of cell adhesion by capping sugar moieties otherwise accepted by the substrate binding step of the enzyme. Thus, the interference with enzyme activity should lead to a pathologic increase in neuron - glial cell adhesion, a phenomenon already described for cell migration in the reeler mutant mice.

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Sievers, J.; F.-W. Pehlemann; S. Gude; D. Hartmann and M. Berry (1994) The development of the radial glial scaffold of the cerebellar cortex from GFAP - positive cells in the external granular layer. **J. Neurocytol.23 : 97 - 115**

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General Research Interests

Is p21ras a master switch to mediate neurotrophic effects in the nervous system?

Not only the protein family of neurotrophins and their receptors but also the diversity of neurotrophin functions has expanded, recently. Neurotrophins (NGF, BDNF, NT-3, NT-4/5) interact with their signalling competent trk tyrosine kinase receptors (trkA, trkB, trkC) showing restricted ligand specificities. In addition all neurotrophins bind to the low-affinity receptor p75 which modulates the function of trk. We characterize the cell type specific intracellular pathways signalling for survival, fiber outgrowth, protection from excytotoxic killing or modulation of synaptic transmission.

We focuss on the elucidation of the neural function of the small GTP/GDP binding protein p21ras. This intracellular membrane anchored protein oscillates between the inactive GDP-bound and the singalling GTP-bound conformation. Transgenic animals expressing activated p21ras selectively in neurons are used to clarify its "neurotrophic" role in central neurons.

Research Project on Glial Cell Structure and Function in Health and Disease

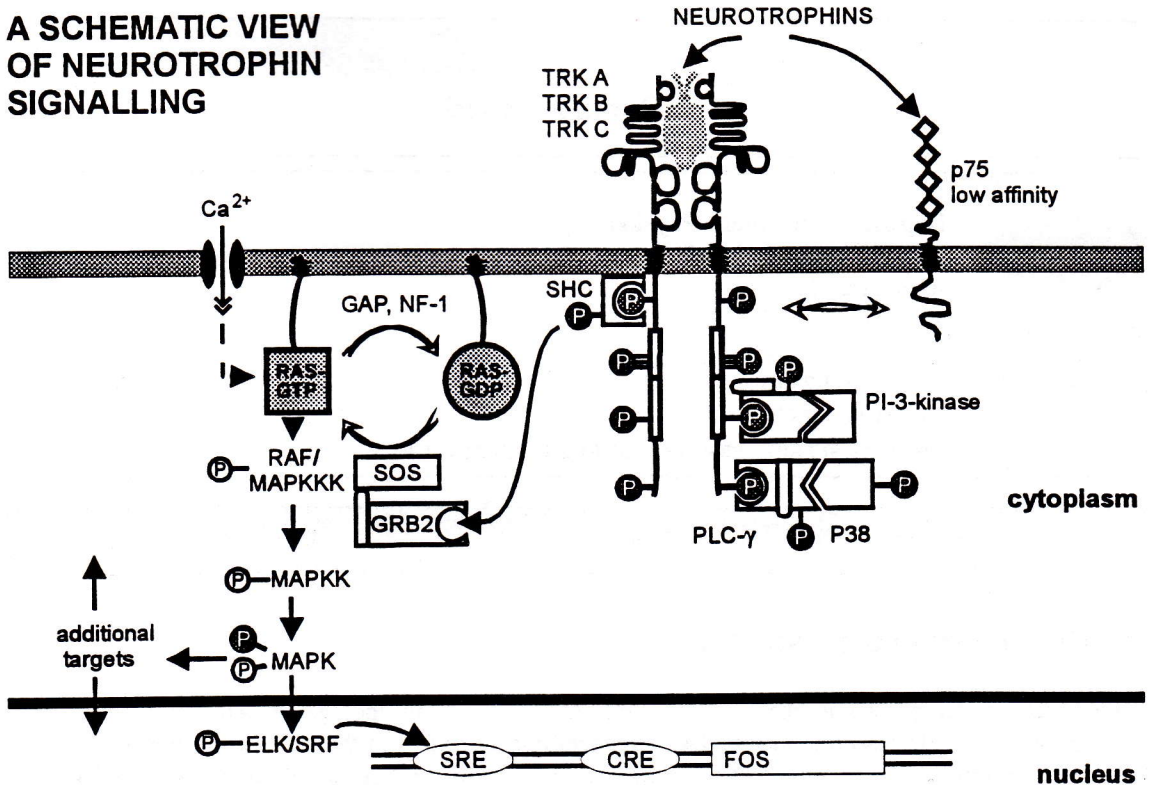
The function of p21ras in pig oligodendrocytes

Recently, H. Althaus et al. have demonstrated that cultured pig oligodendrocytes respond to nerve growth factor by increased DNA-synthesis and by induction of fiber outgrowth. The trk tyrosine kinase receptors are necessary and sufficient to mediate neurotrophin actions. Here we show that pig oligodendrocytes express and regulate trkA mRNA, coding for the signalling competent receptor for NGF. Within 8 days of culture the trkA mRNA levels increased 2.5 fold in the presence of NGF as compared to intreated controls. Similar increases were seen already with in 2 days of NGF treatment. In contrast, the levels of the mRNA coding for the p75 low affinity receptor decreased slightly. These results suggest an autocrine or paracrine enhancement of NGF action on oligodendrocytes. We are now investigating if the NGF induced fiber outgrowth or trkA mRNA regulation is mediated by p21ras activity.

Methods Available

General molecular genetics methods
Neural cell cultures
In *vitro* protein-protein interactions

A SCHEMATIC VIEW OF NEUROTROPHIN SIGNALLING



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General Research Interests

Myelinogenesis in the CNS of trout

The myelin-forming cells in the CNS of trout in terms of morphology as well as their cell lineage relationshsips closely resemble mammalian oligodendrocytes, while in their molecular phenotype including the regulation of myelin gene expression they exhibit striking similarities with mammalian Schwann cells. Furthermore both cell types share a remarkable capacity for remyelination after injury. Since it can be expected that transcriptional mechanisms play a major part in controlling the activity of myelin genes during development and regeneration a detailed characterization of cis-and trans-acting regulatory elements of these genes will be of crucial importance for a better understanding of these processes.

Research Project on Glial Cell Structure and Function in Health and Disease

Molecular structure of genes coding for fish myelin proteins

Myelin in the CNS of fish is exceptional in its protein composition since it contains two P_0-like glycoproteins, termed IP1 and IP2, replacing proteolipid protein. Furthermore a novel major protein constituent of 36,000 dalton apparent molecular weight occurs, which is unique to the CNS myelin of bony fish and for wich as yet no molecular equivalent has been detected in the myelin of other vertebrate classes. To allow for a better understanding of the molecular structures and functional properties of these fish myelin proteins the cDNAs encoding 36K as well as IP1 are being cloned and sequenced. By in situ hybridization and northern blotting the expression of both genes by oligodendrocytes during trout brain development in vivo and under cell culture conditions is comparatively analysed. Furthermore genomic cloning and sequencing is performed to elucidate the structures of the underlying genes. Thereby special emphasis is given to the functional characterization of the promoter regions.

Methods Available

Protein biochemistry including electrophoresis and western blotting
Molecular cloning and sequencing of myelin genes (incl southern and northern blotting)
In situ hybridization and immunohistochemistry
Cell and tissue culture techniques
Whole cell recording with the patch-clamp technique

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General Research Interests

Regulation of Glial Cell Volume and intracellular pH

Glial swelling has long been known to accompany pathophysiological events such as cerebral ischemia, trauma, or metabolic disorders, contributing to brain edema formation and detrimental rises of intracranial pressure. The mechanisms of glial volume homeostasis are not known in detail. So far we have identified various factors causing glial swelling in vitro: exposure to e.c. glutamate, K^+, arachidonic acid, and, best studied, acidosis. Swelling appears to be an active phenomenon, resulting from the activation of homeostatic mechanisms controlling the e.c. environment to facilitate neuronal function. Major elements of the homeostatic machinery include the Na^+/H^+-antiporter, Na^+/HCO_3^--cotransport, lactate transport, and, possibly, H^+-channels. Cell volume regulation is closely linked to intracellular (i.c.) pH-regulation, currently studied under controlled conditions in vitro. In earlier studies we could demonstrate that glial cells from primary culture and C_6 glioma cells (used as model cells, available in large quantities with standardized properties) swell considerably in e.c. acidosis. Swelling required the presence of bicarbonate and Na^+, was 50% inhibited by amiloride, and was believed to result from the activation of transport systems regulating i.c. pH.

Research Project on Glial Cell Structure and Function in Health and Disease

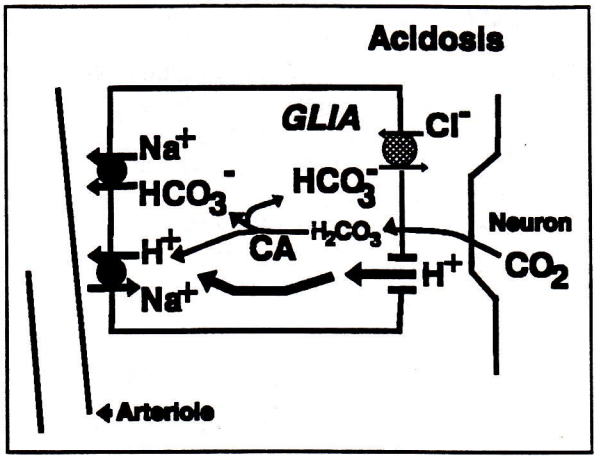
Mechanisms of pH Regulation in Glial Cells

Currently the i.c. pH changes accompanying e.c. acidosis and also the mechanisms involved in pH regulation under physiological conditions are studied under close control of other e.c. factors. It turns out that glial cells acidify in e.c. acidosis. In the absence of bicarbonate, i.c. acidification is slower, but also markedly present. In both cases, realkalization upon e.c. pH normalization is faster than i.c. acidification. Inhibitors of Na^+/H^+ exchange, Cl^-/HCO_3^- exchange, or Na^+/HCO_3^- cotransporter have only minor effects on i.c. acidification, but with the application of inhibitors of H^+-ATPases, such as NEM or NBD-Cl, acidification is significantly increased. NEM causes i.c. acidification under physiological e.c. pH also, indicating that H^+-ATPases contribute to glial pH homeostasis. In vivo, a 'polar' spatial distribution of proton pumps and ion transporters could serve to rapidly extrude acid equivalents to the microcirculation, or even to alkalize the neuronal environment during activity - in brief to cause local pH gradients in the brain. Future efforts will be devoted to verify this hypothesis using in vitro imaging techniques as well as in vivo approaches with an open cranial window technique.

Methods Available

Fluorescence measurements of cytosolic ion concentrations (dual wavelength excitation), cell volume measurements, imaging techniques, video microscopy including image intensifier and averager, cell and tissue culture techniques, histological laboratory, lactate and LDH analysis, fully equipped operating room for small and large animal experiments: laser-Doppler flow, SEP, tissue pO_2, respiratory parameters, acid-base status etc.

Fig. 1:
Hypothetical polar distribution of ion channels and antiporters on certain glial cells supposedly acting as homeostatic elements between neurons and the microcirculation. The proposed polarity would enable the glial cell to communicate early and efficiently changes of neuronal activity to the vascular bed. In vitro the polarity is lost, thus allowing the investigator only to study the net effect of changed e.c. conditions.



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General Research Interests

Transmitter Receptors and Ion Channels on glial cells

For a long time, glial cells were viewed as the electrically passive elements of the central nervous system. Recent advances in imaging and physiological techniques made it possible to demonstrate that glial cells in cell cultures can express a variety of voltage gated ion channels and transmitter receptors. These studies implied that glial cells have the structural repertoire to respond to rapid signals, but have not answered whether these cells indeed do so in an intact nervous system. To address this question, we have developed brain slice preparations and applied the modern imaging and physiological techiques to study individual glial cells. We can identify and analyze properties of microglial cells, oligodendrocytes and their precursors in the corpus callossum, Bergmann glial cells in the cerebellum, astrocytes in the spinal cord, cortex and hippocampus. Our recent studies demonstrate a diversity of physiologically distinct glial cells with receptor properties different from those found in neurons. The aim of these studies is to define the signals between neurons and glial cells and to unravel the contribution of glial cells to the information processing in the central nervous system.

Research Project on Glial Cell Structure and Function in Health and Disease

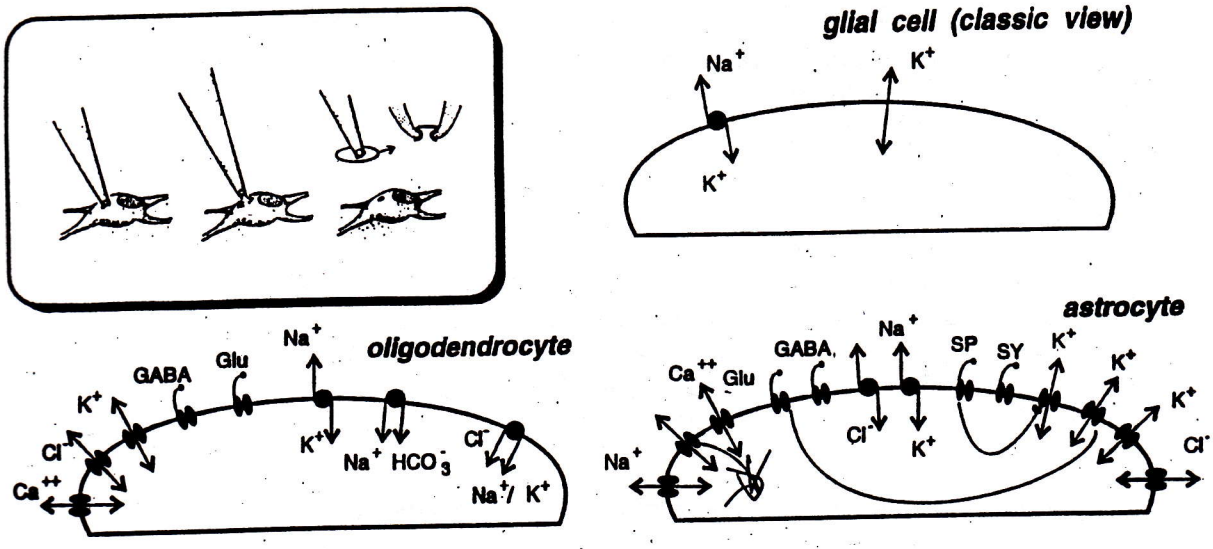
Physiological Properties of Microglial Cells

Microglial cells are considered as a resident macrophage population in the central nervous system. We have studied the physiological properties of microglial cells in culture; based on their membrane channel pattern, we could distinguish these cells, not only from macroglial cells and neurons, but also from non-brain derived macrophages. Such channel pattern was only found in a subpopulation of bon marrow cells, the stem cells of monocytes. Cultured microglial cells have the capacity to respond to neuronal signals; the transmitter ATP induced membrane and cytosolic Ca^{2+} responses in these cells. To overcome the restriction of the cell culture model, we have recorded from comparable cells in brain slices, namely invading, ameboid microglial cells at early postnatal age. These cells show similar physiological properites as their cultured counterparts.

The ameboid microglial cells on the acute brain slice show a characteristic 'behavioural' repertoire such as phagocytosis and defined movements. One aim of the present project is to characterize these behaviours and determine its pharmacological profile. A second goal is to compare the physiological properties of the ameboid with those of the resting microglial cells. Since microglial cells are involved in most, if not all CNS diseases; the study of the influence of signal substances on their behaviour might be a prerequisite to determine their role in the normal and pathologic brain.

Methods Available

Study of single channel and whole cell membrane currents with the patch clamp technique
Use of brain slices to analyze neuron-glia interaction
Fluorescence measurements of cytosolic ion concentrations combined with imaging techniques
Reconstruction of cells with confocal microscopy
Tissue culture techniques



A selection of channels, carriers and receptors described in astrocytes and oligodendrocytes (bottom) as compared to the classical view (top). On the top left, the patch-clamp technique is schematically illustrated.

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General Research Interests

Glial-neuronal interactions in the embryonic CNS of Drosophila

The formation of the CNS axon pattern depends in many aspects on glial-neuronal interactions. We study these processes during *Drosophila* embryogenesis due to the manifold advantages the system offers (genetic analysis, detailed cell biology with many glial cell specific markers, germline transformation etc.). In our work we focus on questions on the determination of cell fate and cell function of embryonic CNS glial cells during axonal patterning. Which genes are required for cell fate decisions? How do the midline glial cells mediate their instructive function during axon pattern formation?

Research Project on Glial Cell Structure and Function in Health and Disease

Analysis of the gene *argos*

We have identified the gene *argos*, which is specifically expressed in the midline glial cells of the embryonic CNS. Molecular and genetic analysis showed that it encodes a secreted, diffusible protein, which is involved in cell fate decisions during *Drosophila* development. To study the function of *argos* during embryogenesis we have isolated a set of X-ray and EMS induced alleles. The genetics of *argos* is complex with at least two closely interacting *argos* like genes in close neighbourhod. The Argos protein is required to control the number of midline glial cells during embryogensis. During midline glia development *argos* is under the control of the glia specific transcription factor encoded by *pointed* which is a nuclear target of a EGF receptor mediated Ras signaling cascade. The present work aims to understand how activation of the EGF-receptor controls *argos* expression during midline glia development by dissection of the *argos* promotor.

Methods Available

- genetics, clonal analyses
- germ line transformation
- molecular biology techniques
- tissue culture techniques
- scanning and transmission electronmicroscopy

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General Research Interests

Electro - Immunological Coupling in Glial Cells

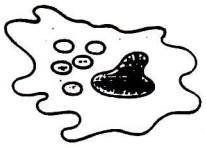
Glial cells, especially microglia and astrocytes are known to participate in immunological processes within the CNS and are able to produce cytokines and present MHC class II antigens. After immunological stimulation, e.g. by leukotriene B_4 or lipopolysaccharides we observed a modulation of ion channels, dependent on intracellular regulatory mechanisms and leading to a marked depolarization of cultured astrocytes. Our main interest is now to clarify the functional relevance of electrophysiological alterations during immunological activation, the underlying ional and intracellular mechanisms and their pharmacological regulation, and the coupling between different immunological stimuli and electrophysiological effects.

Research Project on Glial Cell Structure and Function in Health and Disease

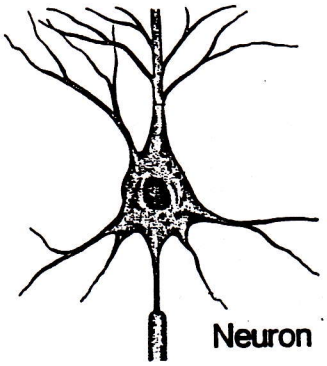
Our research project include the investigation of different immunologically active substances released from macrophages or produced by immunologically competent cells within the CNS like astrocytes or microglia cells concerning their effects on electrophysiological properties of cultured astrocytes and neurons from new-born rats. From these experiments we expect to gain information on the putative role of glial cells for the appearance of neurological symptoms in the course of inflammatory or immunological diseases of the central nervous system. In comparison with these results on rat astrocytes, we plan to study putative effects of immunologically active substances on human astrocytoma cells.

Methods Available

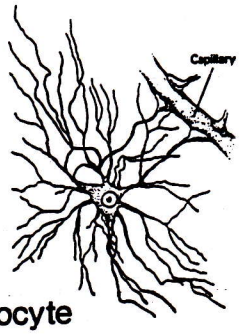
Patch clamp technique, Fluorescence measurements of intracellular ion concentrations (in collaboration with Prof. H. Haas, Düsseldorf), primary cell cultures from CNS (in collaboration with Dr. H.W. Müller, Düsseldorf)



Macrophage



Neuron



Astrocyte

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General Research Interests

I. Glial Cell Proliferation in the brain of adult rodents. Proliferating astroglial, oligodendroglial and (only a few) microglial cells can be found in all areas of the brain of adult unlesioned rodents. Their cell cycle and mode of proliferation were studied in the last years and have led to a quantitative scheme of cell proliferation. We are interested in future to examine how the numerical data of the scheme will be changed (i) after specific wounding and (ii) in mutant mice.

II. Extent of DNA Repair in situ. In untreated animals, the DNA of all cells is continously damaged and subsequently repaired. The rates of DNA damaging and repair are cell type and area specific, possibly due to differences in cell metabolism. In addition to DNA repair capacity (measured as unscheduled DNA synthesis, UDS) we are interested to measure the DNA damaging rate cell type specifically, too. Thus, a balance for each cell type could be obtained demonstrating whether or not unrepaired DNA damage accumulate, as suspected during the process of aging or, e.g., after X-irradiation.

Research Project on Glial Cell Structure and Function in Health and Disease

I. Differentiation of emigrated subependymal cells within the olfactory bulb of adult mice: quantitative aspects

Even in aged rodents many proliferating cells can be seen in the subependymal layer at the border of the lateral ventricle. These cells migrate into the olfactory bulb and differentiate into glial cells (astro- and/or oligodendrocytes?) and also neurons. The time table of differentiation and topographical aspects of the emigration will be analyzed.

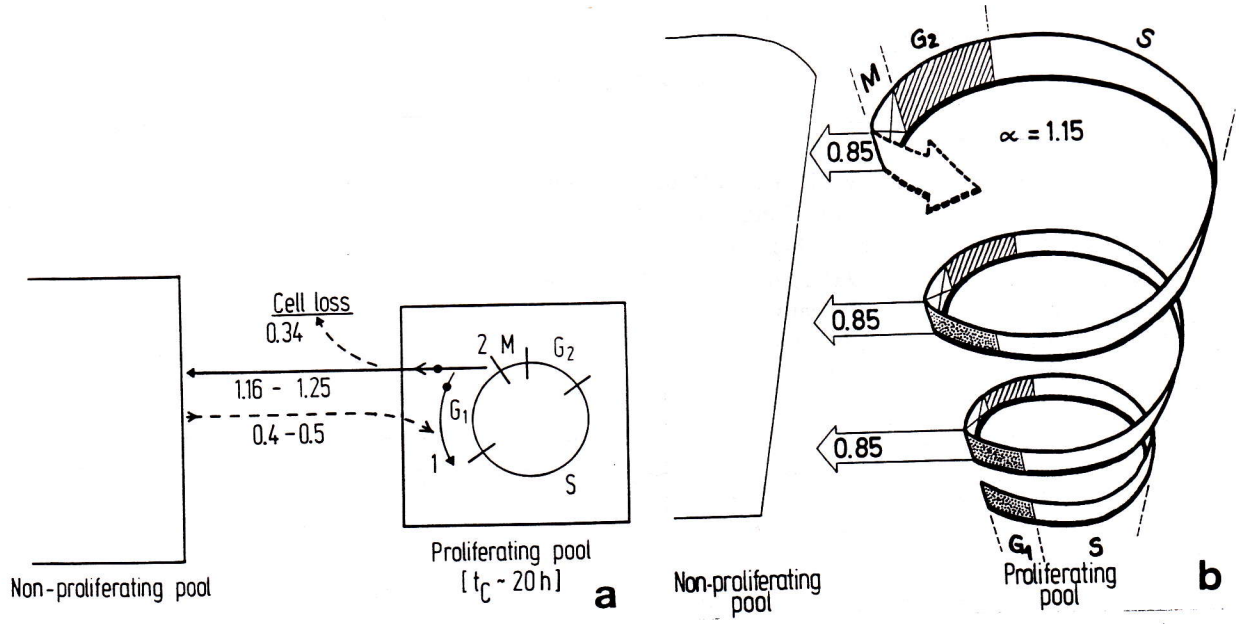
II. Extent of DNA repair of astro- vs. oligodendrocytes during aging

Previous studies showed a decrease of UDS during aging in cortical glial cells (without discrimination of the glial cell types), but not in cerebellar glial cells. It should be clarified whether differences exist among astro- vs. oligodendrocytes.

Methods Available

Quantitative ^{3}H-autoradiography including methods for correction of background, ^{3}H-ß-self-absorption and unequal DNA content of the section volume.

Immunocytochemistry with and without subsequent autoradiography



Scheme of proliferation for (a) astro- and oligodendroglial cells in the brain of the unlesioned adult mouse and (b) untreated rat astroglial cells in vitro at DIV7 and DIV12

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General Research Interests

Resident, resting microglia are ubiquitously distributed in non-overlapping territories in the brain. While relatively little is known about the function of resting microglia, the activation of microglia has been intensively studied. Microglial activation becomes apparent by proliferation, recruitment to the site of injury, immunophenotypical changes (including increased expression of the CR3 complement receptor, MHC Class I and II antigens and the receptors for colony stimulating factors) and their capacity to transform into intrinsic phagocytes. In this laboratory the microglial reaction is primarily studied in the facial nerve axotomy paradigm. This has the advantage of leaving the blood-brain barrier intact, allowing the study of intrinsic microglia only. In addition, microglial reactions (with a similar repertoire of microglial activation changes) have been examined in several other models including ischemia, autoimmune diseases, traumatic and neurotoxic lesions. In summary, microglia form an intrinsic immune defense system of the CNS and are primed at an early stage to participate in CNS immune defense.

Research Project on Glial Cell Structure and Function in Health and Disease

The microglia may be the first cell type to become rapidly activated in response to a pathological stimulus. In recent years we have been especially interested in the signalling events underlying microglial activation in various experimental neuropathologies. In addition we have also been examining morphological and immunophenotypical changes in microglia in aged rats. An approach that is proving of great value for investigating molecular signals involved in microglial activation is the use of natural mutants and "knockout" mice lacking specific genes. We have demonstrated that mice lacking the macrophage colony stimulating factor (M-CSF) show a drastically reduced level of microglial proliferation, indicating that M-CSF is involved in this aspect of microglial activation. This approach is currently being extended to other potential signalling molecules and to components of signal transduction pathways such as transcription factors. Studies on aged rats have shown that the microglia are more readily activated in older animals than in young adults and that the pattern of expression of immunomolecules differs. Aged brains also constitutively contain more macrophages. Current investigations are aimed at establishing whether microglia in old animals are more sensitive, or whether there is a more generally increased sensitivity to injury. Finally, we are using the method of differential display PCR to search for glia-related genes that are activated following neuronal injury.

Methods Available

Light and electron microscopy for standard histology
Immunocytochemistry for light and electron microscopy
Fluorescence microscopy
Cell culture techniques
Molecular biology, including in situ hybridisation

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General Research Interests

Multinuclear in-vivo-NMR-Spectroscopy / NMR-Imaging

In-vivo-NMR spectroscopy of the brain, even if it is done volume selectively, inevitably records metabolites from different cell types because of the intrinsically large volume, which has to be recorded (approx. 1 ml in the case of human brain; several l for rat brain). Therefore, isolated cell cultures are well suited to elucidate the origin of NMR detectable metabolites and to follow-up their metabolism by high resolution multinuclear NMR techniques. Depending upon the desired resolution the spectra are recorded from cell extracts or living cells (embeded in gel threads). For the living organism (rat) we have developed techniques for the fast volume selective spectroscopy (curently a voxel size of 5 l, recording time 3.5 min) to record the transient metabolic stages of experimental brain infarcts and its penumbra. Complementary imaging techniques with diffusion weighted or magnetization transfer weighted images record the simultaneous swelling process. Volume regulation is also studied on cell cultures.

Research Project on Glial Cell Structure and Function in Health and Disease

Multinuclear NMR Studies of Glial Cell Metabolism

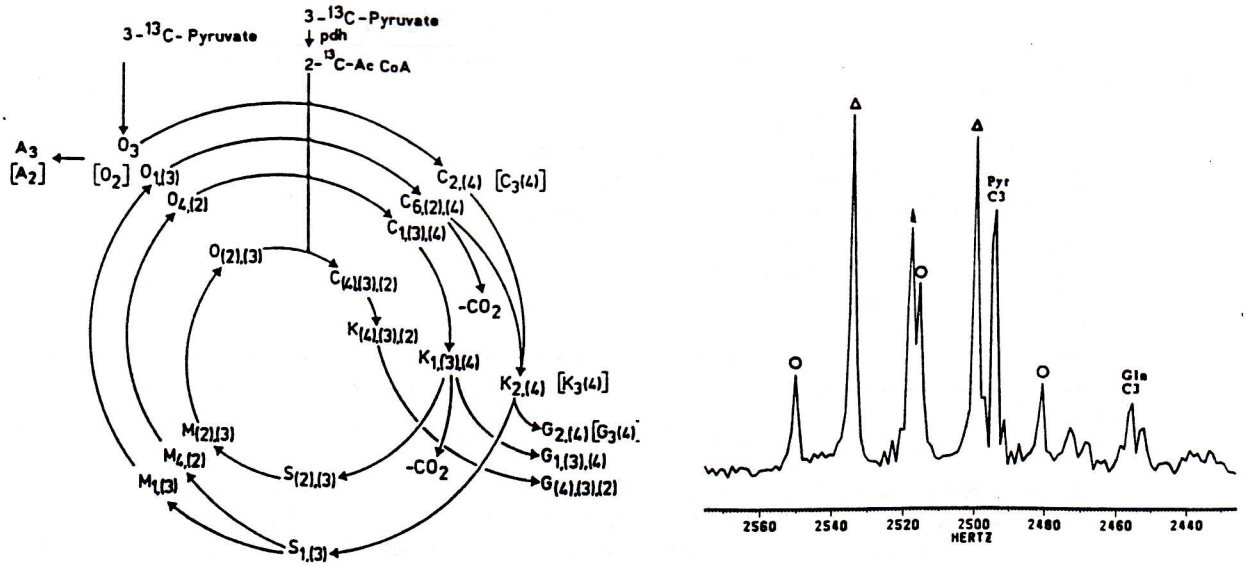
With C-13 labelled precursors (glucose, pyruvate, amino acids etc.) the fate of the label is followed in-situ without metabolite isolation. The relative contribution of various enzymes of glycolysis and the TCA cycle are recorded simultaneously. The metabolic turnover of individual cell types are a prerequisite to understand metabolic traffiquing in brain tissue.

Volume regulation under hyperosmolar and hypoosmolar stress is another key process to maintain neural function. Osmotic stress is therefore induced in cell cultures by external salt concentrations or excitatorial stress. Volume changes are followed-up by diffusion weighted spectroscopy and characterized by quantitative analysis of metabolite concentrations. Of major concern are taurine and myo-inositol for the long term volume regulation.

The NMR method is also used to characterize and quantify membran transport (c.f. pH regulation etc.) and metabolic events after drug treatment.

Methods Available

High resolution NMR spectroscopy (H-1; C-13; P-31; F-19; H-2; N-15)
In-vivo-NMR cell techniques in gel threads
Volume selective NMR spectroscopy in intact organism (SI; CSI)
Fast imaging techniques (diffusion-, MTC weighted images)



a) The fate of the 3-C* label of C-13 pyruvate during utilisation in the TCA-cycle. b) Extended part of the carbon spectrum of C-3 glutamate of C6 glioma cells with the mono-, double- and triple labelled isotopomer.

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General Research Interests

Glia-Neuron Molecular Interactions in Neurological Disease and Regeneration

Neural trauma induces a stereotypic sequence of distinct molecular reactions that reflect the differential expression of specific genes with putative functions in nerve degeneration and repair. To identify such genes we have developed a systematic differential hybridization screening strategy using cDNA libraries of regenerating rat sciatic nerve. A group of 30 regulated sequences could be identified, including 12 novel genes. The isolated genes encode proteins with diverse functions that relate to, e.g., myelination, ion channels, cytokines, growth factor action, RNA-processing and translation, energy metabolism, lipid transport and recycling, cytoskeleton and extracellular matrix formation. It is anticipated that defects of genes with functions related to nerve regeneration could cause developmental and/or degenerative neurological disorders.

We further investigate the capacity of the adult mammalian central nervous system to regenerate after injury using a stereotactic rat brain (postcommissural fornix) lesion model and glial cell suspension transplants.

Finally, we study the expression, function and mechanism of action of neurotrophic proteoglycans and glycosaminoglycans in CNS cell cultures and adult, developing and injured rat brain.

Research Project on Glial Cell Structure and Function in Health and Disease

Peripheral Myelin Protein PMP22. PMP22 is one of the differentially expressed genes in lesioned rat sciatic nerve that could be identified as a candidate gene of a group of hereditary dysmyelinating neuropathies (Charcot-Marie-Tooth 1a, Pressure Neuropathy, Dejerine-Sottas). We currently investigate the cell-biological function of PMP22 and its role in the pathomechanism of PMP22-neuropathies.

Proteoglycans with Neurotrophic Activity. We have isolated and purified a chondroitin sulfate proteoglycan from astroglial and meningeal cell conditioned medium with survival supporting and neurite growth promoting activity for cultured neurons from rat brain. The neurotrophic proteoglycan could be identified as biglycan. Following stereotactic injection into the basal forebrain of rat, biglycan shows significant mnemogenic effects in a passive avoidance learning task. We are interested in the regional distribution, developmental expression, cellular regulation and mechanism of action of this neurotrophic proteoglycan.

Astroglial and Schwann Cell Implantation into Lesioned Rat Brain. The molecular and cellular reactions following fiber tract lesions in the CNS as well as the mechanism of (nonmyelin) axon growth inhibition in the injured brain and spinal cord of adult mammals are not well understood. Using a postcommissural fornix transection model in the rat we investigate the lesion-induced reactions of astrocytes and microglia/ macrophages and the expression and regional distribution of extracellular matrix and cell adhesion molecules (e.g. laminin, tenascin, proteoglycans). Further we investigate the influence of cell suspension implants of juvenile astrocytes and Schwann cells on the capacity of transected fornix fibers to successfully bridge the lesion area and regenerate towards the target (mammillary body).

Methods Available

Gene cloning, differential hybridization screening, PCR, Retroviral gene transfer, In situ hybridization, Immunohistochemistry, Confocal laser fluorescence microscopy, Protein isolation and purification techniques, Biosynthetic protein labeling, Primary nerve cell cultures, Stereotactic brain lesions, Cell transplantations into brain.

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General Research Interests

Molecular genetics of glial cells and myelin formation
The differentiation of myelin forming glial cells provides a model system to study principles of neural development and cellular interactions in the mammalian central nervous system. Myelin assembly depends critically on the coordinate and cell type-specific expression of a set genes which encode the structural myelin proteins. We are using molecular and genetic techniques to study the function of myelin-specific genes in normal brain development and in neurological mutant mice (*jimpy*, *rumpshaker*). These mice display genetic defects of myelination and some have become exact models for equivalent human neurological disorders (*Pelizaeus-Merzbacher disease*). Our major interest focusses on mutations and dosage effects of the proteolipid protein (PLP) gene underlying dysmyelination and abnormal glial cell death.

Research Project on Glial Cell Structure and Function in Health and Disease

Our research is funded by the BMFT and DFG (SFB317, SFB 329). We envision an association with the Schwerpunkt *Functions of Glial Cells* in the future.

Methods Available

cDNA and genomic cloning techniques, immunofluorescence, gene expression analysis, tissue culture techniques, homologous recombination in mouse embryonic stem cells, generation of transgenic mice.

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Schneider, A., Readhead, C., Griffiths, I., and Nave, K.-A. (1995) Dominant-negative action of the *jimpy* mutation in mice complemented with a transgene for myelin proteolipid protein. *Proc. Natl. Acad Sci. USA* , in press.

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General Research Interests

Immune-related Changes of Phagocytic Microglia During Neuronal Degeneration

After lethal neuronal injury the phagocytic microglia induces and modulates immune responses by upregulating the synthesis of surface receptor 3 of the complement (with a crucial role in activating the complement mashinery) and expressing glycoproteins, regulated by the MHC class I and class II genes. In contrast to the sound data gathered on the onset, duration and heterogeneity of the microglial immunophenotypes during microglial activation, almost nothing is known about the fate of microglia after completion of phagocytosis. At least three major questions still await answers: 1) Do the phagocytic microglia migrate away from the lesioned area and if so, to where? 2) Where does the presentation of antigen to T-cells take place? 3) Do the phagocytic microglia stop to express certain antigens, or do they simply die after phagocytosis?

Research Project on Glial Cell Structure and Function in Health and Disease

Fate of Microglia After Completion of Phagocytic Activity

In order to answer these questions we labeled the motoneurons in the lateral facial subnucleus of rats with Fluoro-Gold (FG) and induced microglial neuronophagia by resection of 8-10 mm from the infratemporal facial nerve. The microglia phagocytosed the degenerating motoneurons and took over FG. This enabled a brain-wide unbiased detection and quantification with a computer-aided image analysis system of the FG-labeled microglia (Fig. 1), which showed that the vast majority of them remained within the lesioned nucleus. The important differentiation between microglia and shrunken neurons (both of which are fluorescent) was done by the new method of immunoquenching: staining with neuron-specific enolase (NSE) selectively abolished (quenched) all fluorescence from the prelabeled facial motoneurons and perfectly depicted the FG-containing microglia.

Our next aim is to provide a detailed ultrastructural analysis of the various microglial immunophenotypes during and following neuronophagia. This will be achieved by sequential protocols aimed at a selective quenching of the neuronal and microglial fluorescence in vibratome sections through the brainstem, i.e. by combined incubations with NSE and microglia-specific monoclonal antibodies (OX-42, OX-18, OX-6, etc.), which recognise the various immunophenotypes.

Methods Available

Various peripheral nerve lesions and sutures performed by a trained microsurgeon, Peripheral and intraneural injection of tracing substances, Electrical stimulation of peripheral nerves, Immunocytochemistry, Quantitative fluorescence microscopy with a computer-aided image analysis system, Transmission electron microscopy

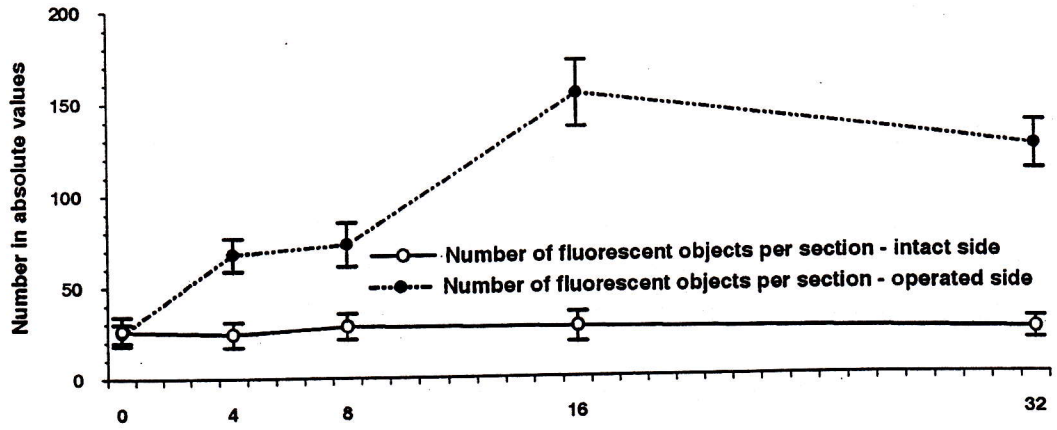

Fig. 1. Time course of the quantitative changes of the phagocytic microglia (fluorescent objects per section) in the Fluoro-Gold prelabeled facial nucleus after resection of the facial nerve.

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General Research Interests

The Subcommissural Organ: An Ependymal Brain Gland

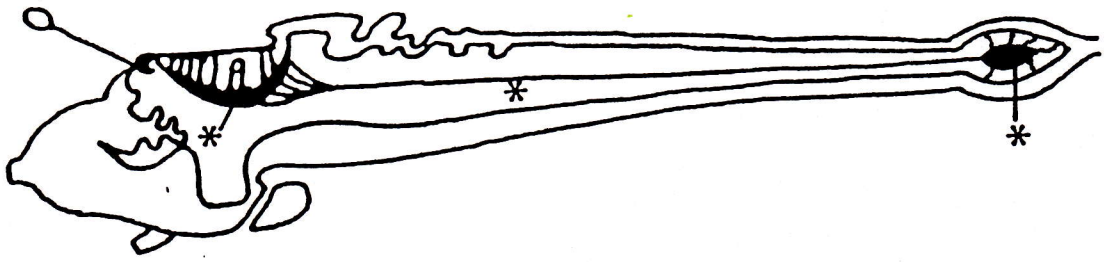
The subcommissural organ (SCO) is a complex of ependymal and ependyma-derived (non-neuronal) secretory cells covering the posterior commissure. In evolutionary terms, the SCO is a very ancient and persistent structure of the vertebrate brain. The cells of the SCO express several of the molecular markers characteristic of tanycytes. The bulk of the secretory products of the SCO, a complex containing different glycoproteins, is released into the ventricular cerebrospinal fluid. In addition, this material also gains access to the blood vessels. In contrast to a remarkable progress in the fine-structural and chemical analysis of the SCO and its secretion (including Reissner's fiber), the biological function of the SCO is still enigmatic.

Research Project on Glial Cell Structure and Function in Health and Disease

We have no project in the present DFG Schwerpunkt. Our investigations have been supported over 8 years by the Volkswagen-Stiftung. We are open with respect to a future association.

Methods Available

Immunocytochemistry
Tracer techniques - Imaging techniques
Confocal laser microscopy - Electron microscopy (TEM, SEM)
Tissue culture techniques
Chemical analysis (E.M. Rodríguez and associates)



Schematic representation of the Subcommissural organ-Reissner's fiber complex (asterisks) in the vertebrate brain (for details see Oksche et al. 1992; Review article).

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General Research Interests

Production of Colony-stimulating Factors by Human Glial Cells

Glial cells are known to produce a battery of polypeptide cytokines that helps them to interact with other cell types of the central nervous system. In the last two years a lot of data have been raised to elucidate this glia-neuron and glia-endothelial cytokine network in physiological conditions and pathological alterations like tumors and inflammation in the central nervous system. A class of polypeptide cytokines that can be produced by glial cells are the colony-stimulating factors (CSFs). The target cells of these factors are inflammatory cells and endothelial cells, which are known to be activated to migrate and proliferate by CSFs.

We have established test systems to assay the production of colony-stimulating factors by glial cells on the mRNA level as well as on the protein level. G-CSF and GM-CSF is inducible in glial cells by inflammatory cytokines like TNF and IL-1. Our recent studies indicate that these cytokines are expressed in high amounts in activated glial cells in inflammatory brain diseases as well as in transformed glial cells.

Research Project on Glial Cell Structure and Function in Health and Disease

Expression of Stem Cell Factor by Astroglial Cells

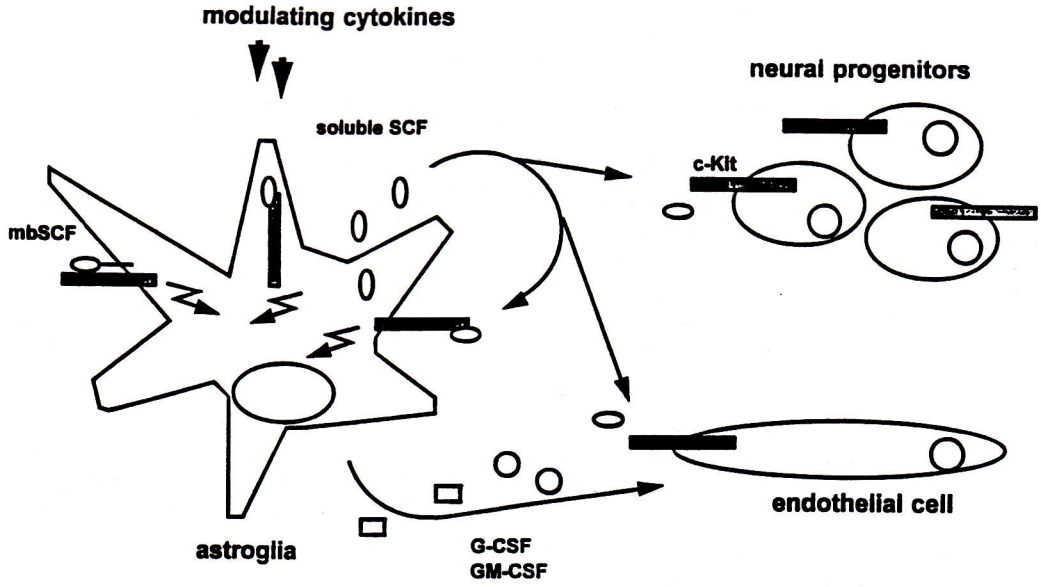
One of these glial cell derived factors first identified as a stimulator of the growth of early hematopoietic progenitor cells termed **stem-cell factor** (SCF) was found to be expressed in the central nervous system by in-situ hybridization techniques. Our group was able to detect expression of SCF mRNA species encoding both for the soluble as well as the membrane bound SCF molecules in glial tumor cell lines as well as in normal cultured glial cells. Furthermore, the cell surface receptor of this factor has been identified to be the ***c-kit*** **proto-oncogene** product, a member of the tyrosine-kinase receptor family. This SCF-receptor is expressed in certain glial cells as well as progenitor cells of the CNS, so that local iuxtracrine as well as autocrine mechanisms via SCF seem likely.

The aim of our studies is to investigate the regulation of SCF expression in glial cells. We have recently identified specific regulators that down- and upregulate SCF expression in fibroblasts and endothelial cells. The soluble as well as membrane bound SCF proteins will be identified using antibodies generated in the last year in our laboratory. SCF expressing and target (SCF receptor expressing) cell types in the CNS will be identified by immunohistochemistry in human brain tissue as well as cultured glial cells. Finally we want to test the hypotheses that glial cells use SCF as an autocrine factor by the addition of rhSCF as well as blocking experiments using neutralizing antibodies and antisense oligonucleotides against SCF and its receptor.

Supported by the Dr. Mildred Scheel Stiftung für Krebsforschung, grant W42/91 Pi1.

Methods Available

Cell culture of normal and malignant glial cells and primitive neural cells
Cytokine assays (bioassays and immunological assays)
Cytokine receptor studies (Binding studies, chemical crosslinking)
Immunophenotyping of glial cells, immunohistology
RT-PCR and Northern blots for G-CSF, GM-CSF, SCF and its receptors



The production of colony-stimulating factors by glial cells is controlled by inflammatory and trophic factors. Target cells for G-CSF, GM-CSF and SCF are known to be brain endothelial cells as well as neural progenitors. Astroglia coexpress soluble and membrane bound (mb) stem cell factor (SCF) and SCF receptors.

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General Research Interests

Molecular and Cellular Mechanisms in Carcinogen-Induced, Cell Lineage-Specific Malignant Transformation and Tumor Progression in the Rat Nervous System

Carcinogenesis is a multistep process interfering with the differentiation program of cells and varying mechanistically with both the type and developmental/differentiation stage of cells and the nature (molecular reactivity) of the carcinogenic agents involved. Accordingly, the magnitude of the neuro-oncogenic effect and the relative proportions of different types of neural tumors induced in the rat by the DNA-reactive carcinogen ethylnitrosourea (EtNU) are strongly dependent on the developmental stage of the nervous system at the time of pulse-exposure to EtNU. Malignant phenotypes ultimately resulting after the initial (mutagenic) interaction of the carcinogen with the target cell system appear to originate from proliferation-competent glial and Schwann precursor cells. Altered control mechanisms of proliferation and differentiation, and abnormal cell-cell and cell-matrix interactions of the "initiated" subset of cells play a crucial role in this process. We are focusing our investigations on genes and molecular control mechanisms critically involved in carcinogen-induced neuro-oncogenesis in a cell lineage-specific way.

Research Project on Glial Cell Structure and Function in Health and Disease

Structure and Function of Differentiation- and Transformation-Associated Genes in the Brain of the Rat

Our project aims at the characterization of genes whose expression, aberrant expression, or inactivation, are critically associated with both differentiation and the process of oncogenesis in the developing nervous system of the rat. Specifically, we intent to analyze with respect to possible mutations and biological function, a gene coding for a cell surface differentiation antigen whose cDNA has recently been sequenced. This glycoprotein ($gp130^{RB13-6}$) is recognized by monoclonal antibody RB13-6 (Kindler-Röhrborn et al., Differentiation 30:53-60, 1985). On prenatal day 18 (the developmental window used for neural tumor induction by pulse-exposure to EtNU) $gp130^{RB13-6}$ is transiently expressed by a small subpopulation of neural precursor cells which differentiate into a subtype of astrocytes, microglia, and ependymal cells *in vitro* (S. Blass-Kampmann, Ph.D. thesis, 1991). However, all of the EtNU-induced brain tumors thus far analyzed express the antigen, as do a collection of 16 malignant cell lines transformed in culture after exposure of fetal brain cells to EtNU *in vivo*; reminiscent of the persistent expression of the mutant *neu (erbB-2)* gene in malignant schwannomas induced by EtNU in the peripheral nervous system of the rat (investigated in a separate project).

Methods Available

Primary cell cultures (CNS and PNS); *In situ* hybridization; Immunocytochemistry; Quantitative immunofluorescence; Electronic multiparameter analysis, cell sorting (FACS); Protein isolation and purification; PCR techniques; Gene cloning and sequencing; microinjection; hybridoma technology; transgenic mice and rats.

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Kindler-Röhrborn, A., S. Blass-Kampmann, K. Lennartz, U. Liepelt, R. Minwegen and M.F. Rajewsky (1994) Surface antigens of cell subpopulations in prenatal rat brain are expressed in a characteristic non-random pattern on their ethylnitrosourea-induced malignant counterparts. Differentiation 57:215-224.

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General Research Interests

Adhesion pathways to regulate axonal growth

A challenging and long-standing goal of developmental neurobiology is to characterize cellular and molecular mechanisms underlying the formation of functional connections between neurons. These synaptic connections are primarily established during embryonic and postnatal development. The molecular signals that influence decisions of axons during extension at choice points include diffusible factors which might act as chemoattractants or as chemorepellant. They might be released by intermediate and final cellular target areas and might have a long-range function. Other molecules providing guidance cues are cell surface and extracellular matrix glycoproteins which might be differentially localized. They might contain permissive and/or non-permissive activities for axonal extension and might have a short-range function.
The molecular analysis of axonal growth has led to the identification of several cell surface glycoproteins belonging to the immunoglobulin (Ig) superfamily. They coexist on many extending axons and show a transient expression pattern during early stages of development. Current research focuses on the interactions of these distinct Ig-like proteins to regulate axonal growth.

Research Project on Glial Cell Structure and Function in Health and Disease

Characterization of tenascin-R (restrictin)

Tenascin-R, previously termed restrictin, is a homotrimeric and homodimeric extracellular matrix glycoprotein synthesized by glial cells and neurons in the developing nervous system. The tenascin-R polypeptide is composed of four structural motifs with similarities to tenascin-C: a cysteine-rich segment at the amino-terminal end, a region with similarity to the epidermal growth factor, several repeats related to a motif found in the extracellular matrix protein fibronectin, and at the carboxy-terminal end a segment related to fibrinogen including a calcium binding site. Tenascin-R was found to bind to the GPI-anchored F11, which belongs to the immunoglobulin superfamily and which is expressed primarily on axonal surfaces. Since the F11 protein has been shown to be implicated in axonal growth by different functional assays, it is conceivable that the interaction between both proteins modulates F11 mediated axonal extension. Current research activities focus therefore on the molecular and cellular analysis of the F11-tenascin-R interaction including the mapping of the binding sites on both proteins.

Methods Available

Protein chemical methods
Tissue culture techniques
Immunological methods including hybridoma technology
DNA recombinant technology

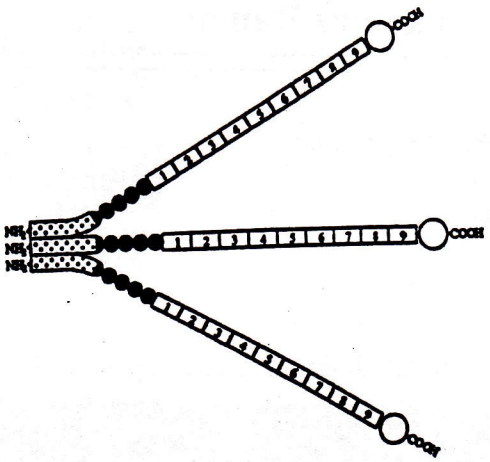

Figure. Structural model of a restrictin homotrimer. The rectangle at the left of each arm represents the cysteine-rich segment which might link monomers into trimers by disulphide bridges. Epidermal growth factor like repeats are drawn as filled circles and the rectangles numbered one to nine represent the fibronectin type III-related domains. The fibrinogen-like segment including a putative calcium-binding site is indicated by an open circle on the right.

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Brümmendorf, T., Hubert, M., Treubert, U., Leuschner, R., Tárnok, A., and Rathjen, F.G. (1993) The axonal recognition molecule F11 is a multifunctional protein: Specific domains mediate interactions with NgCAM and restrictin, Neuron, 10:711-727.

Morales, G., Hubert, M., Brümmendorf, T., Treubert, U., Tárnok, A., and Rathjen, F.G. (1993) Induction of axonal growth by heterophilic interactions between the cell surface recognition proteins F11 and NrCAM/Bravo, Neuron, 11:1113-1122.

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General Reseach Interests

Mechanism and Structure of the Glial Glutamate Transporter

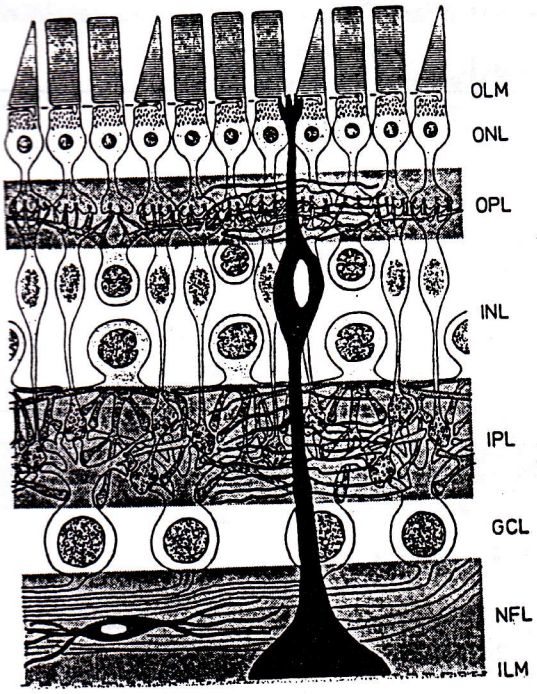
The major part of excitatory neurotransmission in the mammalian central nervous system (CNS) is mediated by L-glutamate. Termination of such neuronal activity is achieved by two sodium-dependent, high affinity uptake systems, one being located in glial cell processes, the other one in presynaptic nerve endings. Both transport systems appear to be of clinical relevance since they represent mechanisms by which synaptically released glutamate is inactivated and kept below toxic levels. The retina provides an excellent model tissue for investigating the pharmacological and molecular properties of both transporter systems since glutamate is the excitatory transmitter used by photoreceptors, bipolar cells and ganglion cells. Conventional astroglia and microglia are present in the retina, but by far the most predominant cell type are the large and radially orientated Müller glia cells which are the predominant glutamate uptake sites in the retina. Our aim is to understand the functional relationship between glial and neuronal glutamate transporters, the regulation of glutamate transporter proteins on the molecular level, and the association of glial glutamate uptake with the glutamatergic systems.

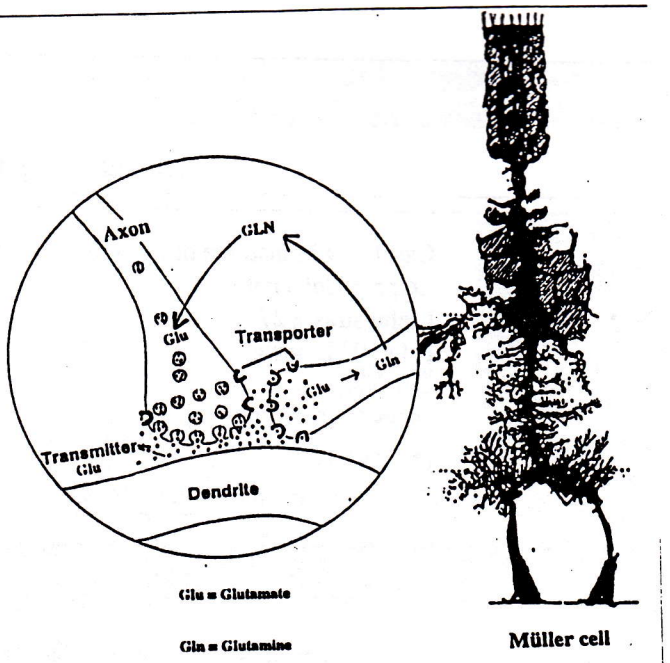
Research Project on Glial Cell Structure and Function in Health and Disease

At the moment our research group does not have a project in the DFG Schwerpunkt: "Functions of Glial cells". However, our research is concerned with the important role of glial cells in maintaining a proper glutamate homoestasis in brain. Therefore, in the near future we plan to submit a proposal.

Methods Available

Histological techniques correlated with light and electron microscopic immunocytochemistry
In situ hybridization, PCR technique
Protein biochemistry including electrophoresis and western blotting
Cell and tissue culture techniques
Studies of transport and metabolism in cultured cells / membrane vesicle preparation





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General Research Interests

Development and Electrophysiology of (Retinal) Glial Cells

The vertebrate retina has been established as a suitable model of the central nervous system. This tissue contains one dominant form of (radial) glia *viz.* the Müller cells. Müller cells are, in the postnatal period, morphologically and immunocytochemically strikingly similar to retinal stem cells, and undergo considerable morphological changes during the period of neuronal retinal network maturation. It has been suggested that the mature phenotype of Müller cells develops by optimal adaptation to neuron-glia interactions. We studied the qualitative and quantitative morphological development of rabbit Müller cells, and the pattern of ion channels and membrane conductivities expressed by adult mammalian Müller cells. Our data demonstrate that postnatal development leads to a Müller cell phenotype that allows for great support of neuronal information processing in the retina. The aim of these studies is to define the signals mediating the development of these "symbiotic" neuron-glia interactions.

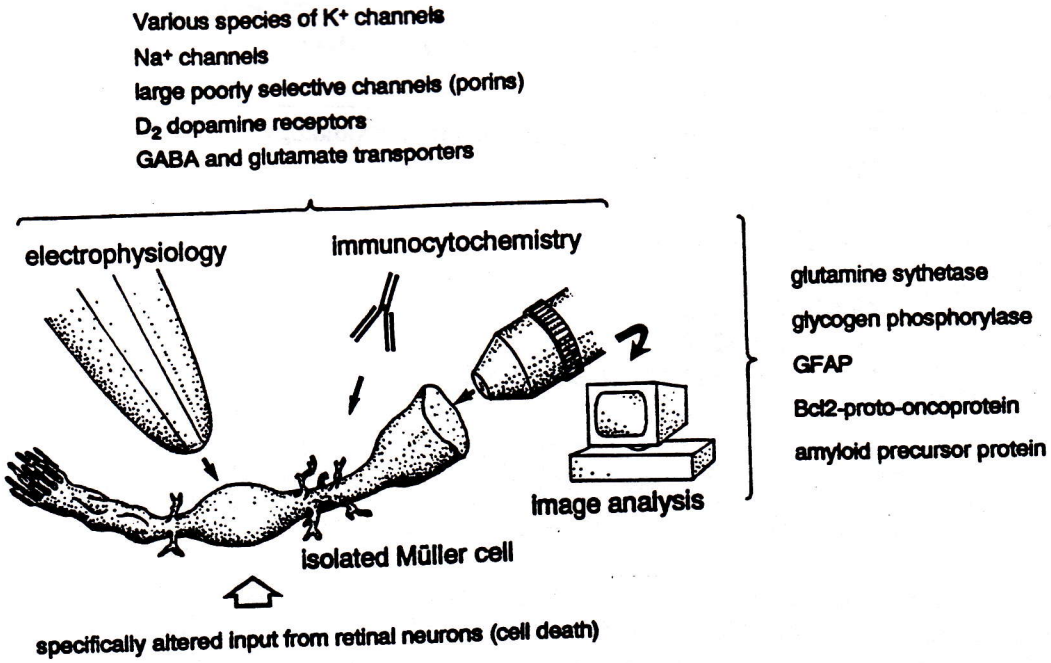
Research Project on Glial Cell Structure and Function in Health and Disease

Types and Topography of Ion Channels, Transmitter Receptors, and Amino Acid Transporters in Glial (Müller) Cells

Own patch-clamp studies on mammalian Müller cells have shown that mammalian Müller cells express at least three different types of voltage-dependent K^+ channels (inward-rectifiers, A current channels, delayed rectifiers), neuron-type Na^+ channels, large poorly selective channels (porins), D_2 dopamine receptors, and electrogenic GABA- and glutamate uptake mechanisms. Furthermore, we got preliminary evidence that the different types of channels, as well as the dopamine receptors, are not randomly distributed across the membrane, but rather form a specialized distribution pattern. One aim of the project is to reveal a "map" of membrane transport protein expression across the adult and developing Müller cell membrane, in order to detect spatio-temporal rules of molecule insertion into the Müller cell membrane. Possible neuron-to-glial signals controlling this program will be tested in cell culture systems, and in animal models where specific populations of retinal neurons are extinguished (mice with photoreceptor cell degeneration [*rd*] or inherited glaucoma accompanied by ganglion cell degeneration). Another goal is to evaluate the genetic identity of the expressed channels and amino acid transporters as recently, several families of genes have been identified that encode different types of voltage-sensitive K^+ channels, as well as GABA and glutamate transporters.

Methods Available

Single-channel and whole cell patch-clamp studies on isolated living cells
Use of retinal wholemounts to analyze neuron-glia interactions
Measurement of glial cell surface complexity with fractal analysis
Immunocytochemistry
Cell and organ culture techniques



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General Research Interests

Development and Differentiation of Glial Cells in vitro

The development of oligodendrocytes in culture is characterized by the coordinated gene-expression of the myelin components. Galactocerebroside appears first, followed by the myelin basic proteins (MBP), the myelin-associated glycoprotein (MAG), the proteolipidprotein (PLP) and the myelin-oligodendrocyte glycoprotein (MOG). Long-term survival of oligodendrocytes requires multiple extracellular signals, and growth factors and cAMP are involved in oligodendrocyte proliferation, survival and differentiation. We have established cell culture systems, using the cerebral hemispheres of newborn rats, to investigate the cellular and molecular mechanisms of the development of rat brain glia cells (oligodendrocytes and astrocytes). In particular, our interest has focused on the organization of cytoskeletal components, the expression of myelin associated glycoproteins and the involvement of second messenger systems during the process of glial cell differentiation in vitro, under normal and stress-induced conditions.

Research Project on Glial Cell Structure and Function in Health and Disease

Signal Transduction Mechanisms and Stress Responses in Glial Cells

Using rat brain glial cells and a recently developed new permanent cell line (OLN-93) with oligodendroglia characterics, we are investigating the factors that control the growth and differentiation of oligodendrocytes, and will study the role of glycoproteins (MOG) in the process of myelin formation. Transcriptional factors, which are activated by growth factors, will be characterized. Futhermore, a major aim of the studies will be to identifiy stress situations in oligodendrocytes, which might cause impairment in the expression of myelin constituents, and thus may have an impact on myelin formation and demyelination processes.

Methods Available

Cell culture techniques
Immunocytochemical methods
Protein analytics (1- and 2-dimensional gel-electrophoresis, Western blotting)
RNA, DNA analytics (Northern, Southern blotting), HPLC-analysis

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General Research Interests

Interaction between Neurons and Glial Cells

The nervous system of the leech consists of a limited number of identifiable neurons and glial cells. Some of these cells are sufficiently large to use ion-sensitive microelectrodes or optical methods to monitor intracellular ion activities or concentrations. Furthermore, the surface of most cell types can be easily exposed, and patch-clamp techniques are applicable. Therefore, the nervous system of the leech is well suited to investigate basic processes of ion regulation in neurons and glial cells as well as the mechanisms by which neurons communicate with each other and/or with the surrounding glial cells. Our research interest is focussed on the membrane mechanisms by which different ions are transported, and on the functional role of neurotransmitter receptors in both neurons and glial cells.

Research Project on Glial Cell Structure and Function in Health and Disease

Functional Role of Neurotransmitters in Intercellular Communication

In recent years we have characterized different receptors for several neurotransmitters such as serotonin, acetylcholine and glutamate in leech neurons and glial cells. These receptors are associated with ion channels, and their stimulation evokes marked changes in the intra- and extracellular concentrations of Na^+, K^+, H^+, Ca^{2+} and Cl^- ions. The neurotransmitter receptors are not homogeneously distributed in the nervous system; e. g., neuropile glial cells as well as moto- and interneurons possess glutamate receptors, whereas sensory neurons are lacking receptors for glutamate. Furthermore, the glutamate receptors in the membranes of glial cells are permeable for Ca^{2+}, whereas those in the neurons are not. By using electrophysiological methods and fluorescent dye techniques we investigate the mechanisms by which neurotransmitters induce the ion activity changes. We will map the distribution of neurotransmitter receptors in the leech nervous system to get more insight into their role in neuron-glial interactions.

Methods Available

* Conventional electrophysiological methods and ion-sensitive microelectrode techniques
* Simultaneous monitoring of two different ions by use of a microscope-based fluorimetric system
* Patch-clamp technique for single channel and whole cell recording
* Histochemistry and autoradiography

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General Research Interests

Properties of glial cells in the developing and mature vertebrate nervous system

We have been interested in the question why the rabbit retina differs from all other known mammalian retinae by the fact that part of their ganglion cell axons become myelinated by oligodendrocytes already within the retina. Usually, oligodendrocytes are prevented from immigrating from the optic nerve into the retina by a barrier at the optic nerve head, the lamina cribrosa. The signals between migrating oligodendrocyte precursor cells and their surrounding tissue (axons, other glial cells, extracellular matrices) needs to be elucidated. Interestingly, oligodendrocyte precursors do not invade the entire rabbit retina, but remain restricted to a wing-shaped area which, after establishement of the myelin, is called medullary ray. No obvious anatomical feature, comparable to a 'lamina cribrosa' is seen. This prompted us to ask how migration and differentiation of oligodendrocytes is initiated and terminated.

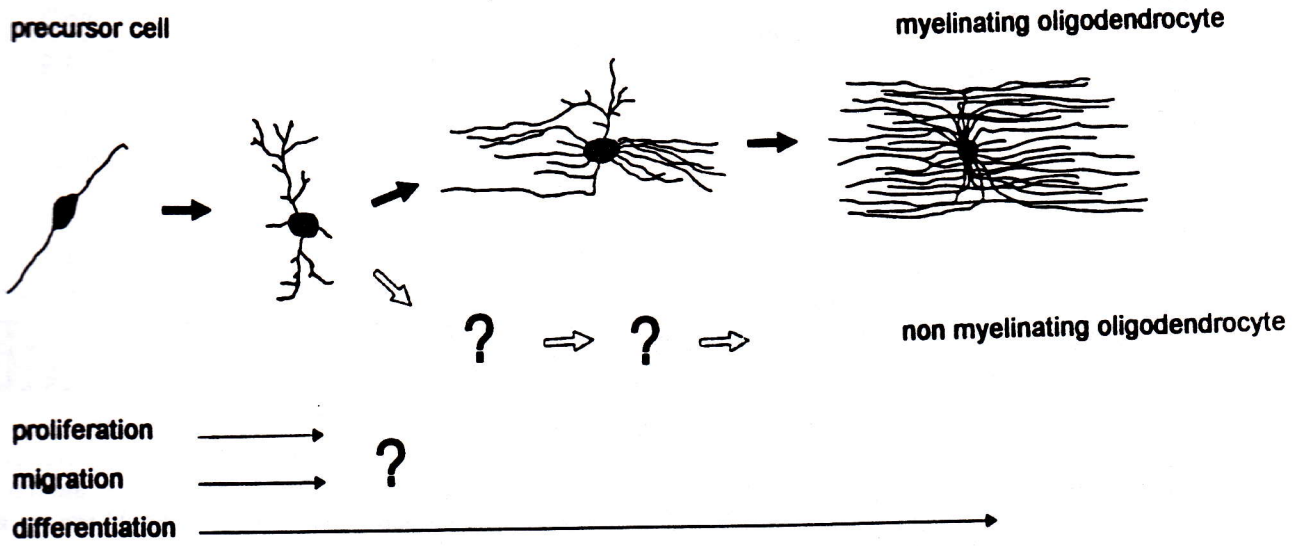
Research Project on Glial Cell Structure and Function in Health and Disease

Differentiation of oligodendrocytes from their precursors

The myelin-producing glial cells of the central nervous system develop during ontogenesis from highly motile precursor cells which in some instances have to migrate over large distances before differentiating. In the past we have asked at what stage of differentiation oligodendrocyte precursor cells are still capable to migrate. The factors influencing the migration of precursor cells are largely obscure. It is unknown why and how oligodendrocyte precursor cells are immobilized at their final destination. One of the aims of our present studies is to address the question how migration of oligodendrocyte precursor cells is initiated, prolonged (what is the nature of their guiding cues?) and terminated, which interactions occur between precursors and their neighboring neuronal elements, glial cells and/or extracellular components. We address these questions presently by analyzing the role of extracellular matrices and neural cell surfaces in conjunction with cell recognition molecules using time lapse video microscopy. In the next step we plan to study the role of transmitter receptors and intracellular signal pathways during migration in intact brain slices. This will be important in understanding why some parts of th central nervous system lack myelination. It might help to understand which cellular processes are necessary to perform successful regeneration.

Methods Available

Tissue culture techniques
Immunocytochemical staining techniques
Transmission electron microscopy
Time lapse video microscopy



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General Research Interests

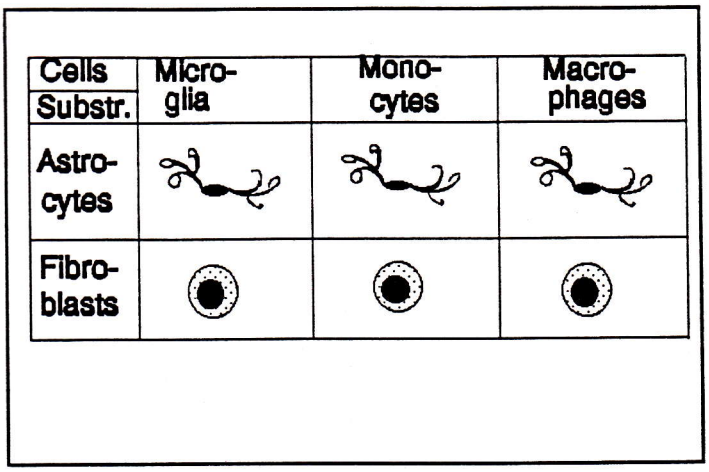
Interactions of astroglia and meningeal cells in development and injury of the nervous system
Radial glia is thought to be important for the placement of neurons in the developing CNS. We have found evidence that the spatial alignment and the differentiation of the radial glial cells are dependent on the contact with meningeal cells which provide spatial cues to induce the formation of the radial glial scaffold and the glia limitans in e.g. the cerebellar cortex and the dentate gyrus. Interactions between astroglia and meningeal cells also take place in traumatic lesions of the CNS, where an accessory glia limitans is formed.
Interactions between astrocytes, microglia and axons
Microglia are resident macrophages of the brain, derived from the myelomonocytic lineage which participate in most pathological reactions of the CNS. They have several distinctive morphological and physiological properties. We have shown that at least the ramified shape and the specific pattern of membrane currents develop only, when microglia are in contact with astrocytes, and also develop, when monocytes and macrophages are cultured on astrocytes. In CNS lesions microglia become activated and interact with regenerating axons. We are interested in the influences microglia have on regenerating axons and are investigating this in vitro.

Research Project on Glial Cell Structure and Function in Health and Disease

Astroglial influences on the differentiation of microglia, monocytes and macrophages
Microglial cells are involved in most pathological states of the nervous system, including aids and Alzheimer's disease. They differ from resident macrophages in other organs by several properties which confer a unique functional versatility to these immuneffector cells. We propose that the distinctive properties of these cells are induced in myelomonocytic precursors by interaction with astroglia, and have so far shown that at least two of the distinct properties of the microglia, i.e. their ramified morphology and membrane currents, are not intrinsic to this subpopulation of macrophages, but are acquired subsequent to their interaction with astroglial cells. We are now interested in studying other aspects of astroglial-microglial interactions and are starting to investigate the mechanisms of the interactions .
Interactions between microglia and axons
In a traumatic CNS lesion activated microglia and macrophages are present in large numbers. Regenerating axons are likely to come in contact with these cells, as they grow through the lesion. In order to gain insight into the influence of the microglia on the regenerative response we studied in vitro the interaction of dorsal root ganglion neurons with microglia and macrophages.

Methods Available

Cell culture of astroglia, microglia, oligodendrocytes, neurons, macrophages from different sources, monocytes.
Tissue culture of brain slices of different ontogenetic stages, retinal explants.
Immunohistochemistry, protein purification, in situ-hybridization, autoradiography.
Time lapse videomicroscopy.



Schematic drawing of the results of cross coculture experiments to test the hypothesis that astroglial cells induce morphological properties specific to microglial cells not only in these cells themselves, but also in monocytes and macrophages. Additionally, physiological properties like the specific pattern of membrane channels are also induced in all three groups of cells by astrocytes.

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Schmidtmayer,J., Jacobsen,C. Miksch,G., and Sievers,J. (1994e) Blood monocytes and spleen macrophages differentiate into microglia-like cells on monolayers of astrocytes: Membrane currents. Glia in press

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General Research Interests

Voltage- and ligand-operated ion channels of central glial cells

Recent studies have indicated that glial cells in cell culture can express a variety of voltage- and ligand-activated ion channels. To test for the presence of membrane channels and receptors on glial cells *in situ* as well as to access neuron-glia interactions we apply the patch-clamp technique to brain slices of the postnatal hippocampus. For cell identification, cells under study are filled with fluorescent dyes during the electrophysiological recordings. In addition, to quantify channel properties in more detail cells were acutely isolated from the same brain areas prior to current analysis. Based on the membrane current pattern, we distinguished at least four different glial cell types in the postnatal hippocampus. These cells express voltage-gated Na^+-, K^+- and Ca^{2+}-channels and receptors for the most abundant neurotransmitters in the brain, GABA and glutamate. Our studies demonstrate differences in the properties of glial transmitter receptors as compared with their neuronal counterparts. We could show that the relative contribution and the pharmacological properties of the investigated currents varied with age which might reflect variable glial functioning in the developing CNS.

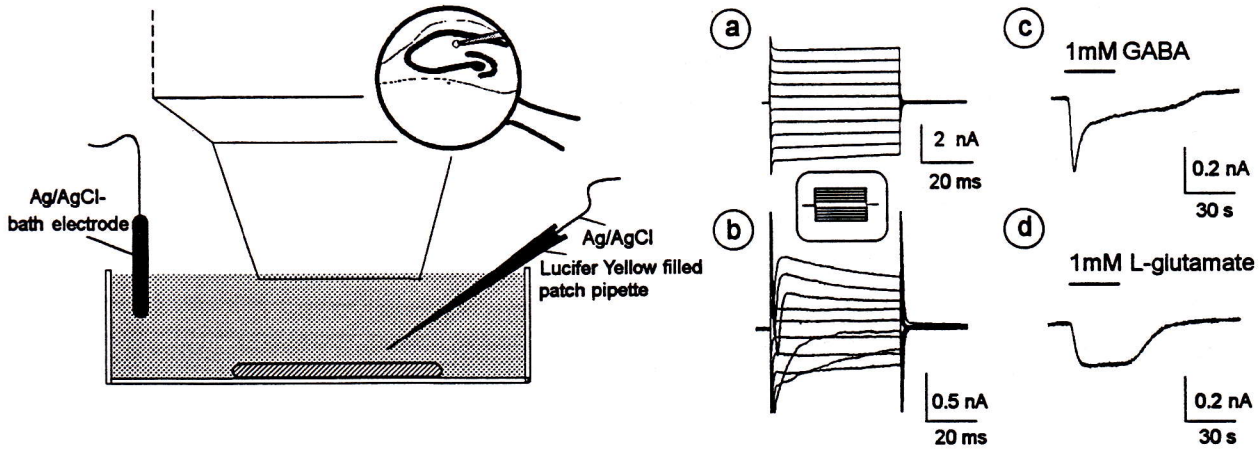
Research Project on Glial Cell Structure and Function in Health and Disease

Neuron-glia interactions

Glial cells lack the ability to generate fast action potentials but they are excitable cells. It seems very likely that they are activated during normal physiological processes. Judging from the *in situ* expression of various glial membrane receptors and the very close association between glial processes and synaptic regions we suppose that glial cells directly influence the information transfer between neurons. To analyze interactions between glial cells and neurons we stimulate neuronal tracts in the hippocampus and simultaneously record corresponding responses in identified neurons and nearby glial cells. We intend to induce long lasting changes in the synaptic efficacy such as LTP or LTD to look whether this change of neuronal activity feeds back onto glial cells.

Methods Available

Membrane current analysis with the patch-clamp technique in situ and in acutely isolated cells
Concentration clamp technique to record transmitter responses with high time resolution
Use of brain slices to analyze neuron-glia interactions
Fluorescence measurements and imaging techniques to estimate cytosolic ion concentrations



On the left side, the application of the pach-clamp technique to hippocampal brain slices is schematically drawn. Glial cells are clamped at a negative holding potential (e.g. -70 mV) and voltage- (a,b) or transmitter-activated membrane currents (c,d) are analyzed.

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General Research Interests

A. Myelin structure
Myelination as developmental process
Dysmyelinoses

B. Glial glutamate transporters

C. Human disease models in the mouse by gene targeting

Research Project on Glial Cell Structure and Function in Health and Disease

Regulation of oligodendrocyte biosyntheses during myelination of
a) myelin proteins and
b) myelin lipids

Synthesis and posttranslational modifications, cellular transport, topology of myelin integral membrane proteins.

Ceramide galactosyl transferase.

Knock out mouse models of myelin protein constituents.

Time- and cell specific knock out of glutamate transporters.

Methods Available

Comprehensive biochemical methods,
molecular biology methods, tissue culture,
transgenic techniques

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General Research Interests

Differentiation of astroglial cells

Astrocytes are important for many different functions of the CNS, i. e. regulation of homoeostasis, of energy, amino acid and lipid metabolism, compartimentation of the CNS, production of neurotrophic factors, metabolism of neuropeptides and transmitters, neuronal guidance, immunological functions etc. Surprisingly this great variety of functions is not reflected by the existence of different types of astrocytes. The astrocyte obviously is characterized by an enormous plasticity. Our studies are intended to investigate this plasticity in the interaction with other cells.

Research Project on Glial Cell Structure and Function in Health and Disease

Differentiation of the glial limiting membrane

At the border of the CNS astrocytes differentiate for the constitution of the superficial glial limiting membrane. This membrane consists of terminal swellings of astrocytic processes, the glial endfeet, and a covering basement membrane. The events leading to the formation of the glia limitans superficialis are largely unknown. However, a similar structure, the accessory glial limiting membrane, only develops in the course of cicatrization after penetrating injuries to the CNS if meningeal cells have previously invaded the wound. Thus, obviously astro-meningeal interactions are important for the formation of the glial limiting membrane.

The aim of our present studies is to characterize astro-meningeal interactions thus to confine the conditions which lead to the formation of the glial limiting membrane.

Methods Available

Tissue culture techniques
Protein chemical methods
Immunocytochemistry
Electronmicroscopy

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Collaboration with Other Teams

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Struckhoff, G. (1994). Cocultures of meningeal and astrocytic cells - a model for the formation of the glial limiting membrane. Submitted.

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General Research Interests

Glial cells in lower vertebrates and axonal regeneration

Glial cells of the vertebrate CNS contribute to success and failure of axonal regeneration. We are particularly interested in the properties of oligodendrocytes in lower vertebrates such as fish and frogs. Both regenerate their axons after transection of the optic nerve suggesting that oligodendrocytes and myelin in the fish and amphibian visual system do not interfere with axonal regrowth.

A characterization of these glial cells and the interaction of growing axons with them is subject of ongoing research.

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Oligodendrocytes derived from the fish optic nerve support axonal growth and regeneration in vitro. When explanted onto goldfish oligodendrocytes even rat retinal ganglion cells successfully regenerate their axons along the surface of these fish glial cells.

Ongoing experiments analyse the contribution of substrate bound and soluble factors made by fish oligodendrocytes on axon growth and cell survival.

Methods Available

- Tissue culture of neurons and glial cells of lower vertebrates and mammals, cross-species neuron glial co-cultures
- Neuronal tracing techniques in vivo
- Time lapse videomicroscopy for studies in vitro and in vivo
- Production of mono- and polyclonal antibodies, immunopurification of proteins
- cDNA-cloning techniques

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General Research Interests

The origin of cell diversity in the CNS

The mechanisms that underly the transformation of the two-dimensional sheet of neural ectoderm into the highly specified three-dimensional nervous system belong to the major unsolved problems in developmental biology. The embryonic development of the CNS involves three principal steps, namely the specification of the neurogenic region of the ectoderm, the specification of metameric units (neuromeres) and their identities and the specification of precursor cell identities within these units (cell lineages). The determination of these regional and cellular qualities is mediated by positional information and cell-communication. We analyze on the cellular as well as molecular level aspects of these processes during early CNS-development of Drosophila.

To investigate the spatial and temporal dynamics as well as the contribution of intrinsic versus extrinsic factors during cell-fate determination we trace the development of individual cells in situ, in vitro and upon heterotopic, heterochronic and heterogenetic transplantations. To identify and characterize genes and their products involved in specific determinative events we use the tools of mutant analysis and molecular genetics.

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Molecular mechanisms underlying glia-determination in the CNS of Drosophila

In order to identify and characterize genes involved in the determination of glial cell types, and to produce cell-specific markers we performed a large scale enhancer-trap screen using the yeast transcription factor GAL4 as a reporter gene. Enhancer traps generated with this construct allow one to express any cloned gene linked to the GAL4 binding site (UAS) in the cells in which a particular GAL4 enhancer trap is active. For a number of lines expressing the reporter in embryonic glial cells we analyzed the spatial and temporal patterns of expression in detail by this providing a comprehensive map of glial cells at the end of embryogenesis.

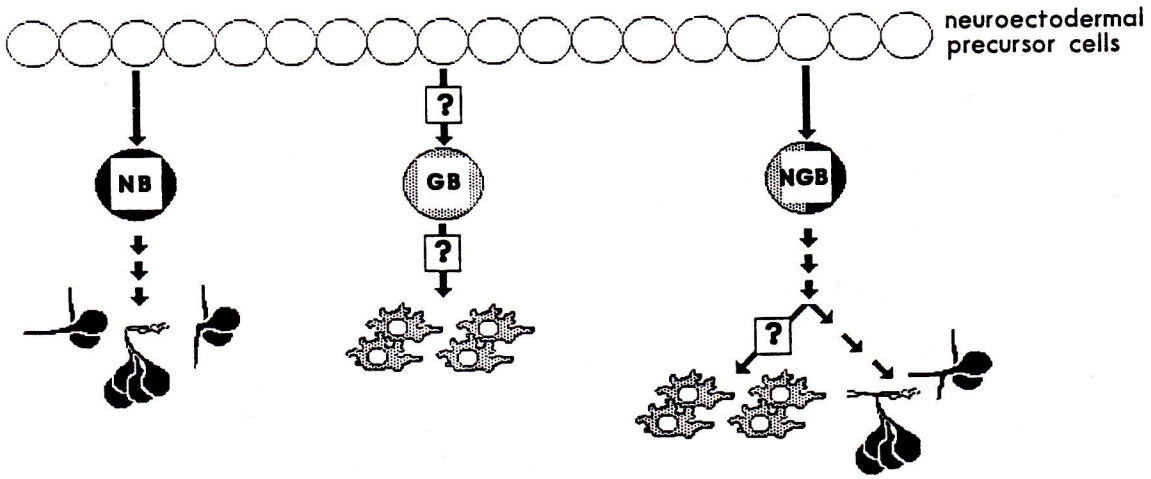
One of these lines carries the P-element insertion in the gene eagle which is expressed in a small subset of neuroblasts and their neuronal and glial progenies. We currently perform a detailed molecular and phenotypical characterization of this gene to clarify its function with respect to glial development. Taking advantage of the GAL4 system we also plan to express certain genes ectopically in the eagle-neuroblasts to investigate their possible role in the neuron/glial cell fate decision.

In collaboration with A. Travers, Cambridge, we have also cloned and analyzed repo, a homeobox gene which is involved in the maintenace and function of most glia. To understand how the glial-specific expression of this gene is achieved we have started to analyze its regulatory region.

Using our enhancer-trap lines we will also investigate additional genes which are presumably involved in glia determination and differentiation.

Methods Available

Labelling of single cells in vivo with lineage tracers (e.g. HRP; DiI); cell transplantations; primary culture of individual cells; immunohistochemistry; time-lapse videomicroscopy and image processing; 3D-reconstructions; genetics; mutagenesis; enhancer-trap techniques; germ line transformation; mosaic analysis; in situ hybridisation; molecular genetics



Three types of precursors segregate as single cells from the insect neurogenic ectoderm: neuroblasts (NB) with pure neuronal progenies, glioblasts (GB) giving rise only to glial cells and neuroglioblasts (NGB) which produce both, neurons and glia. The mechanisms leading to the decision towards glial cell fate are currently unknown and are subject of our investigations.

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General Research Interests

Development and function of myelin-forming Glia

The main focus of the group is the regulation of myelination by oligodendroglial cells and the cellular and molecular mechanisms regulating remyelination of demyelinating lesions. In addition, we are interested in the developmental regulation of the oligodendrocyte lineage in embryonic and adult animals. Prior to forming myelin lamellae, the oligodendroglial precursor cells migrate, proliferate and interact with the axonal surface upon which the myelin sheath is to be laid down. In order to generate sufficient quantity of material to facilitate biochemical analysis of the surface receptors involved in such interactions, we have generated a range of lines of immortalised glial cells using oncogene-carrying replication-defective retroviruses. These cell lines interact with axons *in vitro* and *in vivo* after transplantation into demyelinated lesions. They thus express the spectrum of cell surface receptors required for these specific interactions and can be used as tools to identify these molecules.

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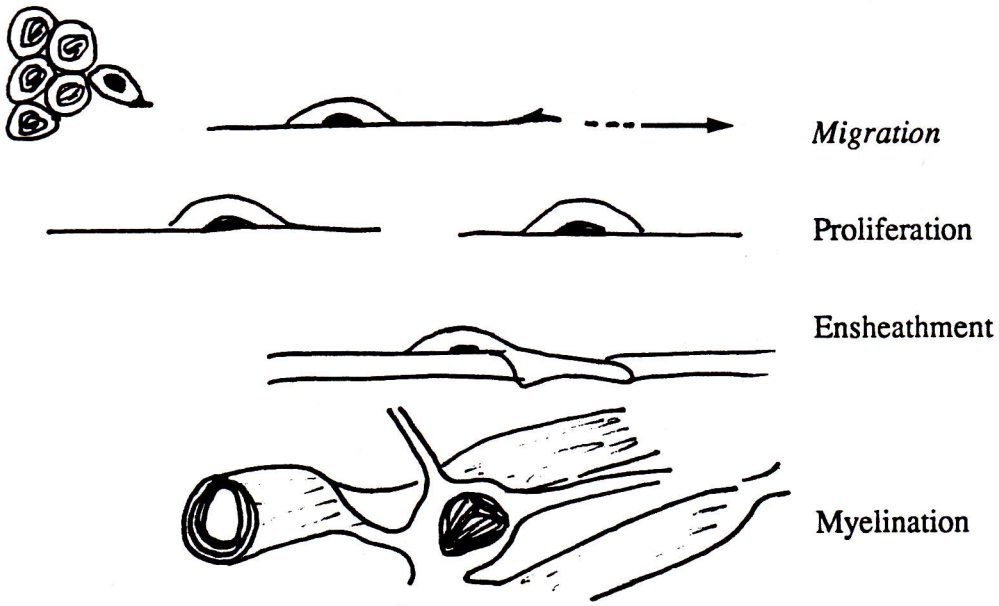
Elucidation of the function of new cell-surface molecules on oligodendrocyte-lineage cells

Since the cell lines described above mimic closely properties of their normal counterparts, we have used them as immunogens for the production of monoclonal antibodies against oligodendroglial cell surfaces. We are especially interested in antigens which are expressed not only in rodents but also in other species including man. We have defined several potentially new surface molecules which are not only useful as markers but may recognise molecules of functional importance involved in specific recognition between neuron and glial cell. In particular, we are focussing on two proteins of 330 and 180 kD which are expressed by oligodendrocyte-lineage cells. We are investigating the function of these molecules by inserting the antibodies in a range of *in vitro* bioassays which assess oligodendrocyte precursor cell migration, proliferation, adhesion to neurons as well as in *in vitro* and *in vivo* models of remyelination. We plan to use expression libraries derived from our cell lines to define the molecular nature of these molecules.

Methods Available

Tissue culture of glial cells and neurons. Standard biochemical techniques. *In vitro* cellular bioassays. Generation of monoclonal antibodies. Use of antibodies to characterise proteins; immunoaffinity isolation. Establishment and screening of cDNA libraries. Use of retroviruses.



Phases in oligodendroglial development

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General Research Interests

Regulation of Gene Expression During Differentiation and Proliferation of Oligodendrocytes

Until reaching their final differentiated phenotype oligodendrocytes undergo a sequence of proliferation, determination and differentiation events each characterized by certain stage-specific marker genes. Expression of these genes is regulated in a spatially and temporally restricted manner by transcription factors which themselves should be differentially active during oligodendrocyte development. We are interested in the identification and functional characterization of transcription factors which are differentially expressed in myelin forming glia cells and could thereby function as regulators of oligodendrocyte development. In addition, we plan to determine the importance of these transcription factors in myelin defects and demyelinating diseases.

Research Project on Glial Cell Structure and Function in Health and Disease

POU Domain Proteins in the Oligodendrocyte Lineage

POU domain proteins are broadly expressed in the vertebrate central nervous system. One of these POU domain proteins known as Tst-1 or SCIP is also expressed in the oligodendrocyte lineage where expression is highest in the undifferentiated state. Down-regulation of Tst-1/SCIP expression coincides with the cessation of proliferation and the onset of myelination, making Tst-1/SCIP a primary candidate for a regulator of oligodendrocyte development. To clarify the function of Tst-1/SCIP we will investigate the influence of Tst-1/SCIP expression on cellular proliferation and glial differentiation using various immortalised oligodendrocyte-derived cell lines as model systems.

Methods Available

cDNA and genomic cloning techniques, tissue culture and gene transfer techniques, immunofluorescence, gene expression analyses

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5 References

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General Research Interests

Growth factors (GFs) in the nervous system (NS)

During the last years about 50 different GFs have been shown to be expressed by, or, to act on cells of the NS. It has become obvious that not only the neurotrophins but also several other GFs may play key roles during development, maintenance/plasticity and de/regenerative processes in the NS. Using a glial (astrocytes) and a neuronal (adrenal chromaffin cells) model system as well as the respective tumor cells (C6 glioma & PC12 cells) we are interested in the following questions: i) Which GFs are expressed simultaneously by a glial cell or a neuron, respectively? ii) Which of the GFs being expressed in the model systems also affects glial cells? iii) What are the differences between the effects of each single GF and their combined action? iv) Are there essential differences in GF-output/action between normal and tumor cells of the NS? v) Are GF-cocktails - instead of single GFs - effective tools for the treatment of neurodegenerative diseases? Our current interest is focused on the complex regulation of fibroblast growth factors (FGFs) and their receptors, the role of the putative GF chromogranin A (CgA), and the development of new transplantation strategies in the treatment of Parkinson's Disease.

Research Project on Glial Cell Structure and Function in Health and Disease

Growth factors in C6 cells

We (and others) have used C6 cells to show that glial cells not only release one or two GFs, but a complex mixture of at least 22 different GFs and related molecules. They also respond to a large number GFs, several of them being expressed by the cells themselves. Analysis of the regulation of expression of FGFs and their receptors revealed a confusing network of interactions between the different GFs as well as their receptors.

Glial/chromaffin cell co-spheroids

It has been shown that, for the treatment of Parkinson's disease (animal models), co-grafts composed of chromaffin and glial cells were significantly more effective than the classical chromaffin cell transplants. One main unresolved problem concerns the viability of the transplants (only few weeks in the case of untransformed cells) versus invasive growth (in the case of tumor cells being grafted). We have established and characterized three-dimensional co-cultures of C6/PC12 cells (or astrocytes/chromaffin cells) which survive for at least more than a year (in vitro) and did not change their size (possibly not invasive).

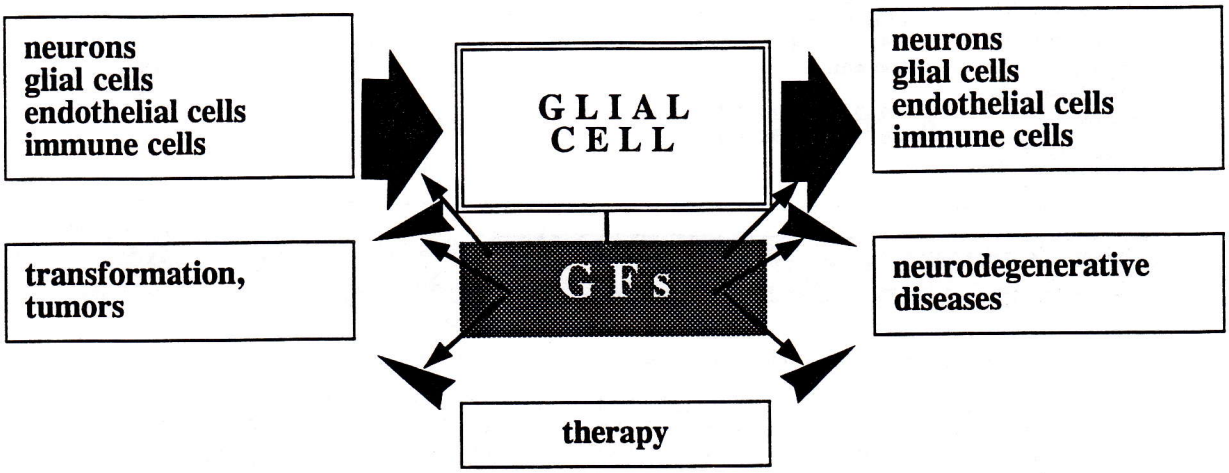
CgA in Schwann- and satellite cells

CgA, a well established protein of unknown function, is widely distributed in the nervous and endocrine system. We have shown that CgA - at least in vitro - has a neurotrophic activity for sensory neurons. Our current investigations show that CgA is expressed not only by neurons, but - during early postnatal development - also by Schwann cells and satellite cells of sensory neurons.

Methods Available

Cell culture: glial & glioma cells, neurons, chromaffin cells, spheroids
Biochemical methods: protein purification and characterization (LC, FPLC, PAGE, IEF)
Immunological methods (antibody production, IHC, Western blots, ELISA, RIA)
Specific growth factor assays: e.g. cell proliferation/survival/differentiation assays
Histological methods: general

Growth factors present in the nervous system are involved in the different cellular communications and interactions. They also may be involved in several pathological aspects. Glial cells - because of their broad spectrum of expression of growth factors and their receptors - may have a key role in this system.



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General Research Interests

Transport Processes in Glial Cells

The plasma membrane of glial cells may be an essential control point within the framework of brain physiology under normal and pathological conditions. Glial cell cultures are an excellent tool for elucidating the properties and functions of glial cells freed from the complexity of the brain as an organ. In cultured glioma cells as well as in glial primary cultures we investigate a variety of transport processes with important functional implications in a) substrate utilization for energy production (glucose, sorbitol, mannose), b) volume and pH regulation (*myo*-inositol, lactate), c) generation of second messengers (*myo*-inositol, arginine), d) substrate channeling from glial cells to neurons (glucose, lactate). The goal of our studies is to describe the mechanism of each of these transport processes and relate them to the contribution of glial cells to the functioning of the brain.

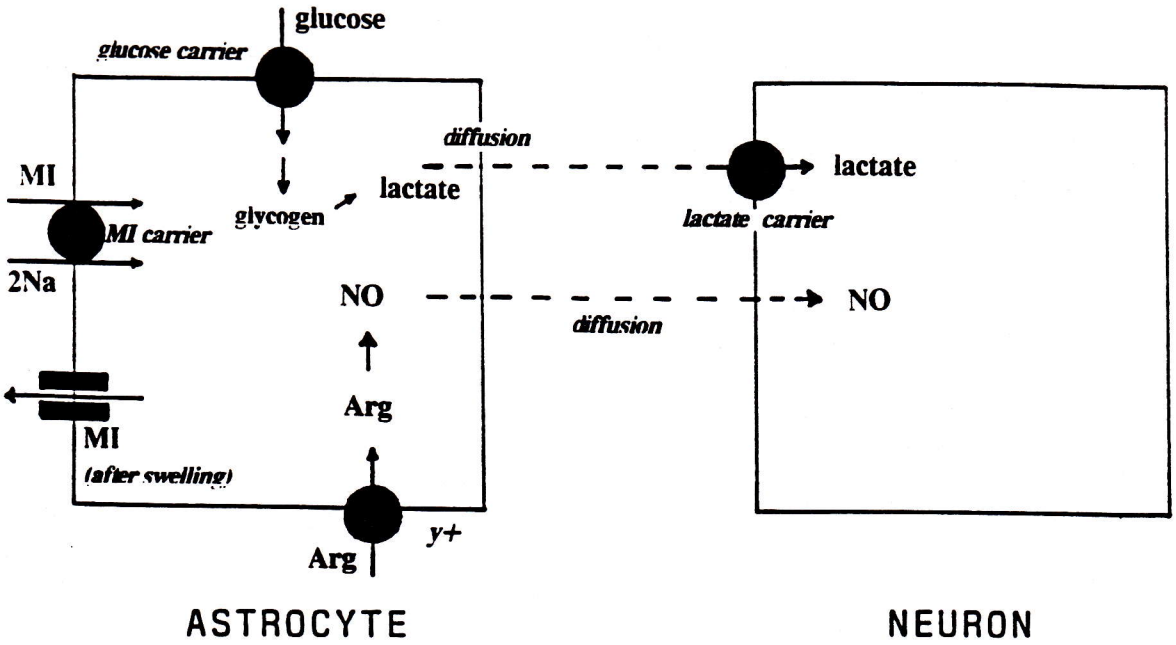
Research Project on Glial Cell Structure and Function in Health and Disease

Transport Across the Astroglial Plasma Membrane: Role in Nourishment of Neurons, Volume Regulation, and Production of Nitric Oxide

1. Transport of lactate in astroglial cells is mainly mediated by diffusion, no evidence for a carrier-mediated process (which was detected in neurons) was obtained. The results agree with the notion of lactate transfer from astrocytes to neurons as part of neuronal energy supply.
2. Transport of *myo*-inositol (MI) in astrocytes consists of two components: a Na^+-dependent, carrier-mediated process at low concentrations of MI is not affected by changes in extracellular osmolarity, whereas a diffusional process, dominant at high concentrations of MI, was found to be increased under hypoosmotic conditions. After pathological cell swelling, increased diffusional release of MI accumulated by the Na^+-dependent carrier may contribute to astroglial regulatory volume decrease.
3. L-Arginine, the substrate of intracellular production of nitric oxide (NO), is taken up into astrocytes with the help of transport system y^+ for basic amino acids. Stimulation of astroglial NO production with bacterial lipopolysaccharide (LPS) was found to lead to an increase in transport capacity for arginine. De novo synthesis of y^+-protein and insertion into the astroglial plasma membrane after challenge of the cells with LPS is suggested. Obviously, a fine tuning of arginine consumption and supply through transport is operating in astrocytes.

Methods Available

Protein purification
Production of antibodies
Cell culture techniques
Immunocytochemistry
Radioactive tracer techniques
Volume determination (Coulter counter)



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General Research Interests

Induction and maintenance of the blood-brain barrier

Brain microvessels are invested mainly by astroglial cell processes. The subendothelial as well as the subpial membranes of astrocytes are occupied by orthogonal arrays of particles (OAPs). Generally, they are believed to carry ionic currents. They are concentrated in membranes adjacent to the basal lamina whereas parenchymal membranes reveal only a very small umber of them. This creates a polarity which belongs to the most remarkable morphological properties of astrocytes in situ.

The blood-brain barrier (BBB) is localized in the tight junctions of the endothelial cells. Astrocytes are believed to participate in the formation of the BBB. In culture, astrocytes or their conditioned medium are able to induce a number of BBB properties, but others including high electrical resistance, low permeability, fine structure of tight junctions, or the expression and distribution of the glucose transporter, are not inducible or maintained by cultured astrocytes. Interestingly, the astrocytes lose their OAP-polarity in vitro.We assume that the loss of polarization in astrocytes correlates to their incapability to induce and maintain the complete set of BBB properties in vitro.

Research Project on Glial Cell Structure and Function in Health and Disease

Membrane properties of the glio-vascular complex

The OAP polarity seems to be established by the synergism of two independent factors or events: 1. The basal lamina is important because OAPs are formed in high density only in contact to a basal lamina. However, the basal lamina alone is not sufficient because it is formed earlier than OAPs. 2. OAP polarity is lost in culture, and glial cells in situ form their polarity only after neuronal activity has established. However, in neurophysiologically active cortex slices, OAPs are present but not polarized presumably because of the absence of a basal lamina. Thus, both the neuronal activity and the basal lamina are prerequisites for the formation of an OAP-related polarity.

The BBB is strictly associated to highly polarized astrocytes. We investigate the tight junctions (TJs) of cultured brain capillary endothelial cells and during development in situ. We distinguish between the complexity of the TJ strands and their association with the P-face (PFA). In situ, the PFA is high, in vitro very low. Cultured astrocytes elevate the complexity of endothelial TJs, but not the PFA. In contrast, epithelial cells maintain their high PFA in vitro. We are interested in both the difference between TJs of epi- and endothelial cells and the requirements of endothelial TJ-PFA. A relationship between TJ-PFA and OAP-polarity in astrocytes is suggested.

Methods Available

Electron microscopy including freeze-fracturing, immunocytochemistry and morphometry

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General Research Interests

Astrocytes are currently regarded as "supporting cells" of central neurons. However, our knowledge is still spurious on the type of neuronal functions supported and on the mechanisms involved. We aim towards a better understanding of astroglial functions by focussing on: (1.) the dynamics of **astroglial lamellae** and astrocytic **gap junctions,** (2.) rapid astroglial **reactions to neuronal signals** induced by remote manipulations and their involvement in lysosomal remodeling of synapses; (3.) the role of astrocytes in **ionic redistribution,** especially chloride ions; (4.) the expression dynamics of **acid phosphatase** and its cell biological roles.

Research Project on Glial Cell Structure and Function in Health and Disease

1.) Determinants of structural development and interindividual variability in astrocytes:

- cell biology of membrane dynamics in astrocytes,
- mechanisms involved in the redistribution of astroglial lamellar processes
- the dynamics of astrocytic membrane coupling by gap junctions.

2.) The role of astrocytes in glia-neuronal interactions that lead to structural plasticity and/orr regression of synapses:

- transneuronal inducibility of structural changes in astrocytes,
- modifications in gene expression in astrocytes

3.) Accumulation of chlorid in astrocytes

- conditions for its induction in acute slice preparations,
- differences in slices of hippocampus, olfactory bulb and olfactory cortex,
- in-situ conditions .

4.) Expression of acid phosphatases in astrocytes

- relation to astrocytic phagocytosis,
- functions in cytosol-cytogel transformation

Methods Available

Glia cell culture, organoid slice cultures of the olfactory bulb, cocultures with olfactory epithelium, LM+EM: enzymehistochemistry, ion histochemistry (chloride), immunohistochemistry, In-situ hybridisation, PCR etc., basic electrophysiology, image analysis.

Members of the Research Team

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Dr. Markus Missler (on leave of absence)
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General Research Interests

Neuron-Glia Interaction

There is substantial evidence that glial cells play a fundamental role in the development of the nervous system serving as guidance or barrier cells for neuronal migration and growth processes. Little is known, however, at the molecular level as to what are basic elements of neuron-glial cell cross-talk during development and following the establishment of synaptic connections in functional plasticity contexts. Our interest has centered on i) cellular selectivity of neuron-glial cell contacts, ii) cell surface constituents of glial cells and their regulation in neuron glial cell contacts and iii) trophic interactions involving the secretion of neurotrophic molecules such as the neurotrophins which also play an important role in neuron-target (neuron) communication.

Research Project on Glial Cell Structure and Function in Health and Disease

Glial cell differentiation and neurotrophic capacities

A series of monoclonal antibodies directed against glial membrane constituents has been developed for glial cell identification and immunoselection. Presently, we are working with mab E1 which defines a cell surface epitope heavily represented on satellite cells and Schwann cells of the PNS (chicken), as well as on GFAP negative CNS glial cells of the astrocyte / oligodendrocyte lineage (mouse) and a number of gliomas (human).
In early development of the PNS, when glial cells as well as neurons display a highly invasive growth behaviour, E1 positive glial cells express receptor for nerve growth factor (NGF) (p75), and react with neurotrophin secretion to picomolar concentrations of NGF. This glia based autocrine neurotrophic circuit is influenced by neurons, and can be envisioned to be an important element of neuron-glial cell cross-talk in nervous system development, regeneration and functional plasticity.

Methods Available

Tissue culture of the nervous system
Cell separation and purification technology
Neuronal growth assays
Immunocytochemistry

Members of the Research Team

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Collaboration with Other Teams

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