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Vortrag 1

Titel:Transcriptional profiling predicts overwhelming homology of adult canine olfactory ensheathing cells, schwann cells, and schwann-like glia

Autoren: Ulrich R.(1),Imbschweiler I.(1),Kalkuhl A.(2),Lehmbecker A.(1),Ziege S.(1),Kegler K.(1),Becker K.(1),Deschl U.(3),Baumgärtner W.(1),Wewetzer K.(4),

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Abstract:
Olfactory ensheathing cells (OECs) which belong to a group of nerve growth factor receptor p75 (NGFR)-expressing cells, including Schwann cells (SCs), and central nervous system Schwann cell-like glia (SG) are considered attractive candidates for cell transplantation-based neural repair. Based on their presence in the olfactory nerves and bulb and their regenerative in vivo effects, it was concluded that OECs have advantages over Schwann cells for central nervous system repair. The aim of the present study was to reveal the molecular phenotype of OECs by means of mRNA microarrays and comparison with SCs, SG, and fibroblasts. Cells were isolated from adult dogs and subjected to mRNA microarray analysis employing canine genome 2.0 arrays (Affymetrix). Canine glial cells were used since they share a number of properties with human cells. Surprisingly, we observed a complete lack of transcriptional differerences between OECs and SG, a close homology of OECs/SG and SCs, and a marked difference between glial cells and fibroblasts. This is in striking contrast to previous mRNA microarray data obtained in rodents. Using supervised clustering with a K-nearest-neighbours algorithm and correlation-based feature selection, we were able to identify cell type-specific biomarkers of OECs and SCs, including aquaporin-1 (AQP1) and stimulator of chondrogenesis-1 (SCRG-1). Immunofluorescence of cultured cells confirmed higher expression of SCRG1 in OECs/SG and of AQP-1 in SCs. Taken together, our data are evidence for a close homology of cultured NGFR-expressing cells at the mRNA level and argue against the idea of a unique molecular setup of OECs.

Kategorie: Lecture

Vortrag 2

Titel:Regulation of hippo pathway in response to retinal damage

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Abstract:
The mammalian retina represents a tissue compartment that does not routinely replenish lost cells and in contrast to teleost fish, the multi-potential progenitor properties of activated Müller glial cells might be blocked by environmental cues. Recently, a novel signaling-network, the Hippo-pathway, was uncovered as a crucial regulator of progenitor cell proliferation regulating organ growth and tissue regeneration. The core of this network is composed of a kinase cascade regulating nuclear localization of the main effector YAP (Yes-associated protein). An active state of the kinase cascade promotes cytoplasmic accumulation and enhances protein turnover of YAP repressing thus regenerative responses that involve stem cell activation. An elevation of nuclear YAP activity, however, could promote the re-constitutive regeneration of certain tissues that otherwise would react with reparative scarring. It is currently not known whether components of the Hippo-YAP cascade – as key progenitor regulators – could have any connection to Müller cells with dormant progenitor properties or would participate in their pathological reactions. In the present study, by mapping the spatio-temporal compartmentalization of YAP and applying a light damage (LD) model of retina in mice, we establish YAP as a novel biomarker of both resting and activated Müller cells. We show furthermore that LD causes a mislocalization of YAP+ cells as part of the remodeling gliotic reaction. Moreover, an elevated YAP protein level paralleled by a lowered expression of its inactive phosphorylated form hints at an activation of YAP signaling and decreased activity of the Hippo kinase cascade in reponse to LD.

Kategorie: Lecture

Vortrag 3

Titel:Topography of lymphatic markers in human anterior uvea

Autoren: Schroedl F.(1),Kaser-Eichberger A.(2),Trost A.(2),Strohmaier C.(2),Bogner B.(2),Runge C.(2),Laimer M.(3),Schlereth S.(4),Heindl L.(4),Reitsamer H.(2),

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Abstract:
Reports of lymphatics in the anterior human uvea are contradictory. This might be caused due to a certain topography which has not been considered yet. Therefore, we here systematically analyze anterior uvea with immunohistochemistry by combining various lymphatic markers. Methods: Human iris and ciliary body were obtained from cornea donors (meeting the declaration of Helsinki). Cross sections of tissue blocks at 12, 3, 6, 9 o`clock position and at all corresponding intersections (i.e., 1.30, 4.30, 7.30, 10.30) were processed for immunohistochemistry of: LYVE1, podoplanin, PROX1, FOXC2, VEGFR3, CCL21. Double-, triple- and quadruple (DAPI)-combination of aforementioned markers were documented using confocal microscopy. Results: In the iris, LYVE 1+ cells were distributed throughout the non-pigmented part. These cells were lacking podoplanin. Numerous podoplanin+ cells were mainly located at the anterior border of the iris. These cells were not colocalized with LYVE1 or PROX1, FOXC2, CCL21, VEGFR3. While podoplanin+ cells were only rarely detected posteriorly of the iris root, many LYVE1+ cells were present within the cilary muscle and ciliary body villi. In the ciliary muscle, occasionally podoplanin+ vessel-like structures were detectable, but these were never co-localized with LYVE-1. Similar vessel-like structures immunoreactive for VEGFR3 never displayed PROX1 or CCL21. A certain topography of structures at the various uvea-positions investigated was not obvious. Conclusion: Structures co-localizing for at least two lymphatic markers were not detectable at positions investigated, and a certain topography was not obvious. Therefore, putative lymphatic channels of the anterior uvea might display a different marker panel than generally presumed, if present at all.

Kategorie: Lecture

Vortrag 4

Titel:The chronically activation of nrf2 in hepatic stellate cells leads to liver fibrosis

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Abstract:
The chronically activation of Nrf2 in hepatic stellate cells leads to liver fibrosis Background & Aims: Nrf2 activity is described to prevent liver fibrosis in various models of chronic liver diseases like we have shown in profibrotic DDC feeding. During liver fibrosis hepatic stellate cells (HSCs; also known as Ito-cells) transdifferentiate into an activated myofibrobast-like cell able to produce excessive extracellular matrix resulting in hepatic liver fibrosis. Methods: A HSC specific knockout of the Nrf2 inhibitor Keap1 mice (GFAP-CreΔKeap1) was used for this study. In these mice Nrf2 is highly activated solely in HSCs. These mice were euthanized and liver tissue was prepared for immunohistochemistry. Sirius-Red staining was conducted to investigate fibrosis, αSMA-staining for HSC-activation, PCNA-staining to estimate proliferation. Results: We found intense bile duct hyperplasia and cyst-formation in the livers of GFAPΔKeap1 knockout mice. Furthermore, HSC-specific Keap1 depletion led to an excessive fibrosis and HSC activation. PCNA staining revealed significantly more proliferating HSC, hepatocytes and cholangiocytes in GFAPΔKeap1 knockout mice. Conclusion: We show here that chronic Nrf2 activation in HSCs has rather a pro-fibrotic and pro-proliferative than a protective function. Given that Nrf2 is chronically activated during liver diseases like alcohol abuses, NASH, and viral hepatitis the role of Nrf2 in this liver diseases has to be reconsidered.

Kategorie: Lecture

Vortrag 5

Titel:Metalloproteases meprin alpha and beta induce collagen typ 1 fibrillogenesis

Autoren: Arnold P.(1),Tredup C.(2),Moali C.(3),David J.S.,Hulmes D.(3),Lucius R.(1),Becker-Pauly C.(2),

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Abstract:
Collagen type 1 is the most abounded structural protein in the human body. It can for example be found in bone, tendon and extra cellular matrix. Malformation of collagen fibers is associated with a large number of diseases such as Ehlers Danlos Syndrom or Osteogenesis imperfect. To mature procollagen it is necessary to remove C- and N-terminal propetides. We were able to demonstrate that Meprin alpha and beta are both capable of doing that. This makes them the first C- and N-propeptidases known so far. Moreover we show a time resolved fiber assembly pattern different for Meprin alpha and beta using transmission electron microscopy. To verify our finding in vivo Meprin alpha and beta deficient mice wer used. We found a lower extra cellular matrix deposition in skin compared to wild type animals with a larger inter fiber space. This results in a ~50% reduced resistance towards physical stress before rupturing. Additionally we could show a connection to Ehlers Danlos Syndrom VII and Osteogenesis Imperfecta.

Kategorie: Lecture

Vortrag 6

Titel:Interplay between nrf2 and amphiregulin during mechanical ventilation

Autoren: Fragoulis A.(1),Reiss L.(2),Siegl S.(2),Pufe T.(1),Uhlig S.(2),Wruck C.(1),

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Abstract:
Rationale: Mechanical ventilation (MV) elicits complex and clinically relevant cellular responses in the lungs. The current study was designed to define the role of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), a major regulator of the cellular antioxidant defense system, in the pulmonary response to MV. Methods: Nrf2 activity was quantified in ventilated isolated perfused mouse lungs (IPL). Regulation of amphiregulin (AREG) was investigated in BEAS-2B cells with inactivated Nrf2 or Keap1, the inhibitor of Nrf2, by using a luciferase vector with AREG promoter. AREG-dependent Nrf2 activity was examined in BEAS-2B cells, murine precision cut lung slices (PCLS) and IPL. Finally, Nrf2 knockout and wild-type mice were ventilated to investigate the interplay between Nrf2 and AREG during MV in vivo. Lung functions and inflammatory parameters were measured. Results: Nrf2 was activated in a ventilation-dependent manner. The knockdown of Nrf2 and Keap1 via shRNA in BEAS-2B cells as well as an EMSA with lung tissue revealed that AREG is regulated by Nrf2. Vice versa, AREG application induced a significant Nrf2 activation in BEAS-2B cells, PCLS and IPL. The signal transduction of ventilation-induced Nrf2 activation was shown to be p38 MAPK-dependent. Finally, in vivo ventilation experiments indicated that AREG is regulated by Nrf2 during MV. Conclusions: We conclude that the Areg expression is regulated by Nrf2. During high pressure ventilation Nrf2 becomes activated, and induces AREG leading to a positive feedback loop between Nrf2 and AREG, which involves the p38 MAPK and results in the expression of cytoprotective genes.

Kategorie: Lecture

Vortrag 7

Titel:Towards characterization and functional elucidation of polycomb repressive complex 1 members in human neural differentiation

Autoren: Thomas R.(1),Su T.(1),Hindley C.(1),Davis J.(1),Pruszak J.(1),

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Abstract:
In order to translate human stem cell biology to biomedical paradigms including regenerative medicine, advanced insights into the fine-tuning of cellular growth control and phenotype establishment are necessary. Polycomb group (PcG) proteins are epigenetic modifiers capable of silencing gene expression by means of histone trimethylation and monoubiquitination. The polycomb repressive complex 1 (PRC1) members chromobox homolog-2 (CBX2), CBX4 and CBX7 have been shown to be critical for controlling pluripotency and for regulating lineage-specific patterns of gene expression in development as well as in cancer. Their role in human neural differentiation remains poorly understood. Using embryonic and induced pluripotent stem cell derived neural cells as well as cancer cell lines, we generated a comprehensive profile of these and other PRC1 members in four independent systems of human neural differentiation at the mRNA (qRT-PCR) and protein level (western blot, immunocytochemistry, flow cytometry). We found that CBX7 shows a maintained expression in cells of human neural lineage development including neural stem cells and post-mitotic neurons, contrasting its key role in maintenance of pluripotency in murine embryonic stem cells and thus warranting further analysis into its context-specific function and regulation.

Kategorie: Lecture

Vortrag 8

Titel:A critical phase for synaptic integration of adult newborn hippocampal granule cells

Autoren: Schwarzacher S.(1),Jungenitz T.(1),Beining M.(1),Radic T.(1), Jedlicka P.(1),

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Abstract:
Authors Stephan W. Schwarzacher, Tassilo Jungenitz, Marcel Beining, Tijana Radic Institute of Clinical Neuroanatomy, Goethe-University, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany A critical phase for synaptic integration of adult newborn hippocampal granule cells Adult neurogenesis of dentate gyrus granule cells has been found important for specific forms of hippocampal learning and memory. At present, it is heavily debated, at which time point of their development and maturation newly generated granule cells may contribute to this novel form of adult brain plasticity. We used retrovirally mediated expression of GFP in combination with high frequency stimulation of the perforant path to analyze morphological prerequisites for functional integration of adult newborn granule cells into the adult rat hippocampus. High frequency stimulation elicited long term potentiation together with expression of the immediate early gene Arc, a marker for synaptic plasticity, in almost 100% of mature granule cells. In contrast, newborn granule cells showed only partial activation with increasing numbers of Arc-positive cells between the third and the fifth week. The populations of Arc positive and Arc negative cells allowed the comparison of age-matched cells within the same specimen. Complete dendritic trees were imaged at a two-photon microscope and reconstructed from the volume stacks.We found structural differences in soma location and dendritic spanning field, as well as spine numbers. In summary, we show, that the majority of newborn granule cells are integrated into the hippocampal network between the third and the fifth week. Supported by DFG (CRC 1080, TP A3).

Kategorie: Lecture

Vortrag 9

Titel:Granulovacuolar degeneration of neurons in a mouse model of tauopathy

Autoren:Köhler C.(1),Midani(1),Dinekov(1),Götz(2),

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Abstract:
Granulovacuolar degeneration (GVD) is a neurodegenerative change that appears as vacuolar lesions containing a central granule. Neurons affected with GVD are found in Alzheimer's disease (AD), but to a lesser extent also in other neurological diseases. The CA1 region of the hippocampus and the adjacent subiculum are predominately affected. Early studies on human autopsy cases showed that in AD the degree of GVD exceeds that of age-matched controls manifold, although the frequency and severity of GVD increases with normal aging. Recently, a staging system has been established for GVD and it has been proposed to be the fourth histopathological sign of AD. Only few experimental data on GVD exist. Transgenic pR5 mice express the longest human tau isoform together with the pathogenic mutation P301L and are an established model of tauopathy. Tau is hyperphosphorylated in many telencephalic neurons already in young pR5 mice, but only a subset of neurons in old pR5 mice develops an advanced stage of tau hyperphosphorylation and tau fibrillary pathology. We found that this subset of pR5 neurons displays granulovacuolar lesions together with a phospho-epitope signature of an advanced stage of tau hyperphosphorylation, but granulovacuolar lesions were rarely seen in neurons containing mature tangles. We confirmed the GVD nature of the granulovacuolar lesions by immunolabeling with established GVD markers. Neurons displaying GVD were only exceptionally seen in old non-transgenic littermates. We show the age-related appearance of GVD and relationship to tau pathology in the amygdala, subiculum and cornu ammonis of pR5 mice.

Kategorie: Lecture

Vortrag 10

Titel:The balance of id3 and e47 determines bmp-induced adult neural stem cell differentiation into astrocytes after vascular damage

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Abstract:
Adult neural stem cells (NSCs) of the subventricular zone (SVZ) are an endogenous source for neuronal replacement in CNS disease, but adult neurogenesis is compromised after brain injury in favor of a glial cell fate. The failure of NSCs to differentiate into neurons after brain injury has been attributed to changes in the NSC environment, such as elevated levels of bone morphogenetic proteins (BMPs). However, it is unknown how this unfavorable extracellular environment translates into an intrinsic transcriptional program that regulates NSC differentiation. Our study reveals that the transcriptional regulator inhibitor of DNA binding 3 (Id3) regulates BMP-induced adult NSC differentiation into astrocytes via control of the basic helix-loop-helix transcription factor E47. Genetic depletion of Id3 in mice increases the number of SVZ-derived neurons in the olfactory bulb and decreases the number of astrocytes generated from adult NSCs at the rostral end of the rostral migratory stream and the cortical lesion center after traumatic brain injury. Furthermore, NSCs isolated from adult Id3-/- mice fail to differentiate into BMP-induced astrocytes, while E47-deficient NSCs readily differentiate into astrocytes in the absence of BMP. Further analysis revealed that E47 represses the expression of astrocyte-specific genes in adult NSCs. These results identify Id3 as the BMP-induced transcriptional regulator, promoting adult NSC differentiation into astrocytes upon CNS injury and reveal a molecular link between environmental changes and NSC differentiation in the CNS after injury.

Kategorie: Lecture

Vortrag 11

Titel:Oligodenrocytic stress responses and their impact on brain intrinsic inflammation

Autoren:Clarner T.(1),Janssen K.(1),Victor M.(1),Fragoulis A.(2),Draheim T.(1),Wruck C.(2),Pufe T.(2),Beyer C.(1),Kipp M.(1),

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Abstract:
The loss of oligodendrocytes within foci of reactive gliosis and the presence of recruited immune cells are characteristic for Multiple Sclerosis (MS) lesions. While a plethora of studies have investigated molecular events operant during the establishment of inflammatory MS foci, our knowledge about the sequence of events that is active within oligodendrocytes and surrounding astrocytes is in its infant state. Using the cuprizone model, we aimed to identify (i) the key-players executing oligodendrocyte death, (ii) operant oligodendrocyte-intrinsic cytoprotective pathways and (iii) oligodendrocyte-derived factors orchestrating cell-cell interactions during early MS lesion development. In vivo luciferase imaging of Nrf2/ARE-–system activity showed that oxidative stress is a characteristic and early feature of this model. Genome-wide array analyses and confocal laser scanning microscopy revealed that the induction of an unfolding protein response (UPR) is selectively induced in oligodendrocytes, but not other glia cells. Experiments using knock-out animals clearly demonstrated that the UPR-related transcription factor Chop/Ddit3 mediates oligodendrocyte apoptosis. While oligodendrocyte-intrinsic cytoprotective mechanisms appear to be insufficient to rescue oligodendrocytes, activation of the cytoprotective Nrf2-pathway in surrounding astrocytes is critical for oligodendrocyte protection, as evidenced by lower number of apoptotic oligodendrocytes in animals where the Nrf2-inhibitor Keap1 is selectively deleted in Gfap-expressing cells. Finally, we show that (i) UPR induction is paralleled by increased levels of Cxcl10, and that (ii) astrocytes and oligodendrocytes in concert are able to modulate early microglia responses in a Cxcl10-dependant manner. Future experiments have to show which factors regulate oligodendrocyte-astrocyte crosstalk in this model.

Kategorie: Lecture

Vortrag 12

Titel:Repeated subpial cortical demyelination in a rat model of multiple sclerosis

Autoren: Garea-Rodriguez E.(1),Wegner C.(2),Neid K.(2),Thal D.(3),Krieglstein K.(4),Brück W.(2),Stadelmann C.(2),Merkler D.(5),

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Abstract:
Cortical remyelination represents an important self-repair mechanism in demyelinating diseases such as multiple sclerosis (MS). However, cortical MS lesions frequently fail to remyelinate, especially at later stages of the disease. The aim of the study was to determine whether repetitive demyelinating episodes may exhaust the intrinsic cortical remyelinating capacity. Therefore, MS-like lesions were induced in the rat targeted cortical experimental autoimmune encephalomyelitis (EAE) model in a repeated manner. Furthermore, we compared oligodendroglial loss in subpial cortical demyelination (SCD) in early and chronic MS. Our data indicate efficient oligodendroglial repopulation in subpial cortical lesions in rats after repeated demyelination that was similar to early, but not chronic MS cases. Four cycles of experimental de- and remyelination were not sufficient to induce sustained remyelination failure as found in chronic cortical MS lesions. This suggests that alternative mechanisms contribute to oligodendrocyte depletion in chronic cortical demyelination in MS.

Kategorie: Lecture

Vortrag 13

Titel:Atomic force microscopy as a potent tool for biomechanical tissue probing

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Abstract:
In recent years, scientists have become increasingly aware of the potential inherent in atomic force microscopy (AFM) to examine Youngâ€™s modulus in ocular and other tissues. With this method, it is possible to set regions of interest on a microscopic specimen and to probe the biomechanical tissue properties therein. Different types of tissue can be selected and compared within a sample. Also, gradients of Youngâ€™s modulus within tissue can be revealed. We used an AFM force mapping technique to generate continuous Youngâ€™s modulus depth profiles in porcine corneas after riboflavin/UVA-induced collagen crosslinking (CXL). We disclosed an exponential decrease in standard CXL efficacy with increasing stromal depth. We also showed that an efficient, CXL-driven increase in corneal strength is restricted to the anterior 200 Âµm if the standard CXL technique (involving epithelial debridement and instillation of riboflavin on the exposed stroma) is used. Similar studies are being conducted on porcine corneas after femtosecond laser-assisted transepithelial CXL, where the corneal epithelium remains intact and riboflavin is administered through an intrastromal pocket. Preliminary data already indicate that the depth-dependent distribution of CXL efficacy follows a markedly different pattern. Firstly, the depth-dependent decline of Youngâ€™s modulus is not exponential. Secondly, the zone of effective CXL apparently reaches through the entire cornea. We therefore speculate that femtosecond laser-assisted CXL is an effective alternative to the standard method. With these examples, we would like to advertise the high potential inherent in AFM force mapping for biomechanical tissue investigation on a microscopical scale.

Kategorie: Lecture

Vortrag 14

Titel:Targeting of tail-anchored proteins to peroxisomes and mitochondria in mammalian cells

Autoren: Islinger M.(1),Costello J.(2),Camoes F.(3),Gomes S.(3),Bonekamp N.(3),Almeida M.(3),Castro I.(2),Ribeiro D.(3),Schrader M.(2),

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Abstract:
Tail-anchored (TA) proteins – a diverse group of proteins with multiple functions – are characterized by a single membrane-spanning helix at the C-terminus which anchors them to the membranes of peroxisomes, mitochondria and the endoplasmic reticulum (ER). The systems involved in targeting TA proteins to the ER rely on the GET-protein pathway whereas the mechanisms for mitochondria and peroxisomes are less clear. Further complexity has recently emerged with evidence that there are TA proteins targeted to both organelles. To assess how extensive sharing of TA proteins between organelles is, we tested a number of mitochondrial TA proteins for peroxisomal association. This revealed a number of candidates which were both peroxisomal and mitochondrial. Additionally, exclusively peroxisomal proteins were identified which, in the absence of peroxisomes, were targeted to mitochondria. One of these, ACBD5, was analyzed further to dissect the properties which contribute to organelle targeting. ACBD5 targeting to peroxisomes is dependent upon a highly charged region following the membrane-spanning helix. Stepwise replacement of positively charged with hydrophobic residues, led to mistargeting, initially to the mitochondria, and finally to the ER. Targeting to peroxisomes appears to be dependent upon Pex19. As shown for the interaction between Pex19 and ACBD5, subtle polarity changes at the TA proteins' tail modulate the affinity to the receptor resulting in differential targeting. Our findings indicate that the sharing of membrane components between peroxisomes and mitochondria is more prevalent than previously thought and that targeting of TA proteins to either organelle is achieved by charge differences in the tail region.

Kategorie: Lecture

Vortrag 15

Titel:Valves along the epididymal duct - luminal segmentation of the epididymis

Autoren: Stammler A.(1),Hau T.(1),Middendorff R.(1),

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Abstract:
The epididymal transports sperm over a distance of several meters within a few days, mediated by epididymal mechanisms. The luminal content flows through the duct and passes by distinct epithelial surfaces in each segment. Depending on surface interactions the spermatozoa are modified in a specific manner. Segmentation of the epididymis has been described previously based on (i) distinct epithelial morphology, (ii) distinct gene expression pattern, and (iii) restriction of the interstitial space by connective tissue septa (CTS). The epididymal duct is a continuous tube with the luminal space considered to be without boundaries. However, our experiments with perfusion of the luminal space using tracer-suspensions revealed obstacles along the epididymal duct, suggesting a kind of valves along the duct correlating with the localization of segment boundaries. Epididymal segments are able to resist high luminal pressure without influencing nearby segments when perfusing with a constant flow rate in an antero- or retrograde manner. Time lapse investigations of intraluminal tracer injection impressively showed a constant swelling of perfused segment without penetrating following segments. The valve eventually releases a surge of tracer-suspension only after a dramatic increase of pressure, resulting in filling up the entire adjacent segment within minutes. The morphological and/or functional basis of these “valves” is unknown so far. We speculate, however, whether (i) the duct is narrowed by connective tissue at the CTS, (ii) the duct has a specific folding, (iii) valve function is due to contractions. Our data suggest new concepts of luminal segmentation along the epididymal duct which could be relevant for sperm maturation and ascending infections. Grant: Land Hessen LOEWE MIBIE, A3

Kategorie: Lecture

Vortrag 16

Titel:Time-lapse imaging reveals different contraction patterns in seminiferous tubules of rodents and men

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Abstract:
The contractile function of testicular peritubular cells and the epididymal smooth muscle cell layer is well orchestrated to ensure transport of spermatozoa. By enabling maturation of spermatozoa with acquisition of fertilizing capacity and motility, contractile cell function in both organs, testis and epididymis, supports male fertility. To assess the role of various signaling pathways, we developed a time-lapse imaging approach to visualize contractions of seminiferous tubules and the epididymal duct as well as sperm transport. This ex vivo approach allowed imaging under near-physiological conditions. In rat epididymal duct, time-lapse imaging detected a pattern of regular phasic contractions which elicited movement of intraluminal contents. In contrast, irregular and undulating wall movements were observed in rat seminiferous tubules and could be transformed into characteristic frequency spectra by Fourier analysis. These spectra were affected by cGMP signaling which shifted the frequency spectrum towards slower frequencies. Moreover, data suggest that differential contractile patterns characterized by distinct frequency spectra may be related to different spermatogenic stages. In human seminiferous tubules, time-lapse imaging revealed very slow contractions ressembling a peristaltic wave that induced sperm transport. In case of fibrotic changes and disturbed spermatogenesis, these contractions seem to be absent. Time-lapse imaging enables the study and visualization of contractile cell function and sperm transport in testis and epididymis under near-physiological conditions. It is a feasible technique that allows to evaluate the influence of various drugs and signaling pathways in epididymal and testicular contractile cells.

Kategorie: Lecture

Vortrag 17

Titel:Multiple sites of chemosensation in the murine trachea

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Abstract:
Recently, we have identified taste receptors (Tas2R) on cholinergic brush cells as a mechanism to detect potentially harmful substances (hazardous substances, bacterial products). Thus, Tas2R operate in addition to pattern recognition receptors. Utilizing the molecular components of the canonical bitter taste transduction cascade, brush cells evoke protective respiratory reflexes. Here, we address the hypothesis that “taste recognition” is present on multiple sites in the airways. In the mouse trachea, mTas2R108 is detected in the brush cell population. Isolated tracheal brush cells respond to its ligand denatonium by an increase in [Ca2+]i. Using ACh biosensors, we found that denatonium elicited secretion of ACh. Application of bitter substances to the tracheal mucosa of spontaneously breathing mice resulted in induction of two different types of generalized avoidance reflexes: decrease of respiratory rate (RR), that was sensitive to nicotinic AChR inhibition, and short periods of apnea that were even augmented by mecamylamine. This was suggestive for direct activation of intraepithelial sensory nerve fibers. Indeed, vagal and spinal ganglia sensory neurons expressed mRNA for Tas2R108 and responded to denatonium (10 mM) by an increase in [Ca2+]i. Inhalative challenge of the whole lung with denatonium caused an increase in airway pressure that was dose- and application mode-dependent and sensitive to muscarinic AChR inhibition. In conclusion, bitter chemosensation acts at multiple sites in the murine trachea to detect harmful components in the mucosal lining fluid. Airway epithelial brush cells mediate reduction in respiratory rate involving cholinergic transmission. Direct activation of sensory neurons modulates parasympathetic bronchoconstriction.

Kategorie: Lecture

Vortrag 18

Titel:Mouse aortic adventitia-derived macrophages and their influence on vascular remodeling and the differentiation capacity of vessel wall-resident stem- and progenitor cells

Autoren:Allmanritter J.(1),Bauer J.(1), Eckner G.(2),Hübner S.(2),Ergün S.(2),

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Abstract:
The paradigm of bone-marrow as the only origin of monocytes and macrophages has been reconsidered in the last years. Among different other cell types macrophages can additionally be generated from stem- and progenitor cells resident in vascular adventitia. We studied the impact of adventitial-derived macrophages on vascular remodeling and sprouting capacity using adult mouse aorta. To this aim aortic ring assay (ARA) was performed with and without clodronate-mediated macrophage depletion. Furthermore, aortic rings were treated with the VEGFR-2 inhibitor Lenvatinib (E7080). Macrophages were detected by immunostaining for F 4/80. Furthermore, immunohistochemical studies were performed for CD31, CD34, CD44, alpha-SMA, VEGF, Ly6c and iNOS. In contrast to freshly isolated aorta, after ARA macrophages were distinctly detectable in the aortic adventitial and the subintimal zones. These locally generated macrophages exhibited a high level of VEGF production. Clodronate treatment reproducible depleted macrophages in the adventitia whereas subintimal localization was not always affected. The number of CD44(+) cells among sprouting and partially cords forming cells was significantly reduced after macrophage depletion. Remarkably, the generally disappearing CD34-staining pattern of the aortic vasculogenic zone after ARA was significantly conserved in absence of macrophages and after Lenvatinib treatment. In conclusion our results suggest that macrophages derived from adult aortic adventitia are involved in the remodeling of the vascular stem cell niche altering the aortic sprouting activity. Macrophage depletion and Lenvatinib treatment identify VEGF produced by aortic adventitia-derived macrophages as a major player of the observed vessel wall remodeling.

Kategorie: Lecture

Vortrag 19

Titel:Denervation-induced dendritic atrophy of dentate granule cells can be prevented by sphingosine-1-phosphate receptor antagonists

Autoren:Vlachos A.(1),Willems L.(1),Becker D.(1),Zahn N.(1),Scholich K.(2),Deller T.(1),

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Abstract:
Denervation-induced remodeling of neuronal dendrites occurs in the context of many neurological diseases. The temporal dynamics and the molecular regulation of these cellular changes are incompletely understood. Here, we used the entorhinal denervation in vitro model to assess the role of Sphingosine-1-phosphate (S1P), a candidate signaling molecule. Time-lapse microscopy of GFP-positive granule cells in organotypic entorhino-hippocampal slice cultures prepared from Thy1-GFP mice was employed to follow dendritic changes for a period of up to 6 weeks after deafferentation. A set of slice cultures was treated with FTY720 (Fingolimod) or the S1P receptor antagonist VPC23019. In untreated cultures profound changes in dendritic dynamics were observed following entorhinal deafferentation: dendritic elongation and retraction events were markedly increased, resulting in a net reduction of total dendritic length (TDL) during the first two weeks after denervation, followed by a gradual recovery in TDL. FTY720- and VPC23019-treatment prevented the denervation-induced net retraction of dendrites, while having no apparent effect on dendritic dynamics in non-denervated control cultures. We conclude that inhibition of S1P receptor signaling promotes dendritic stability in deafferented neuronal networks and prevents the loss of dendrites. These results suggest that neural S1P receptor modulation could be a promising new target in the treatment of neurological diseases (supported by LOEWE-program Lipid Signaling Forschungszentrum Frankfurt and DFG).

Kategorie: Lecture

Vortrag 20

Titel:The neocortex of the reeler mouse – variable cortical phenotypes question the model of a uniform reelin function

Autoren: Wagener R.(1),Mingo Moreno N.(1),Staiger J.(1),

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Abstract:
The extracellular glycoprotein reelin and its various functions play a key role in cortical development. Theories of the precise mechanism of reelin during cortical development are based, to a big extent, on the phenotype of a mouse mutant showing a homozygous null mutation of the reelin gene (reeler mouse). We analyzed cortical development in the absence of reelin starting with the process of preplate splitting, assessed the layer formation at different developmental stages with thymidine analogs and made detailed quantifications of the layering pattern in the adult brain. For the latter, we made use of layer specific mRNA expression, and performed in situ hybridizations for various laminar markers, that were analyzed in different cortical areas. Contrary to the still prevailing view of an inversion of layers, we found that neurons with different laminar fates are mixed up and become distributed all over the cortical thickness. However, the distribution of neurons does not seem to be random. With combinations of the different techniques we could identify distinct phenotypes in different cortical areas. For example, cells in the adult somatosensory cortex show massive intermingling of layer II/III and IV fated cells, that are sandwiched by layer V and VI fated cells. The visual cortex on the contrary, despite of its massive intermingling, showed at least a tendency of an inversion of the main laminar compartments. Thus, the role of the glycoprotein reelin in cortical development should be reassessed and its different effects on neuronal migration in different cortical areas should be considered.

Kategorie: Lecture

Vortrag 21

Titel:Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse ca1 pyramidal neurons

Autoren:Lenz M.(1),Platschek S.(1),Priesemann V.(2),Becker D.(1),Willems L.(1),Ziemann U.(3),Deller T.(1),Müller-Dahlhaus F.(3),Jedlicka P.(1),Vlachos A.(1),

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Abstract:
Repetitive transcranial magnetic stimulation (rTMS) of the human brain leads to long-lasting changes in cortical excitability. It has recently gained relevance as a therapeutic tool in neurological and neuropsychiatric disorders associated with alterations in cortical excitability. However, the cellular and molecular mechanisms which underlie rTMS-induced plasticity remain incompletely understood. Here, we employed repetitive magnetic stimulation (rMS) of mouse entorhino-hippocampal slice cultures to study rMS-induced plasticity of excitatory postsynapses in CA1 pyramidal neurons. By using whole-cell patch-clamp recordings, local electrical stimulations and immunostainings for the glutamate receptor subunit GluA1 we found evidence for a preferential potentiation of excitatory synapses on proximal dendrites of CA1 pyramidal neurons (2 - 4 h after stimulation). This rMS-induced synaptic potentiation required the activation of voltage-gated sodium channels (VGSCs), L-type voltage-gated calcium channels (L-VGCCs) and N-methyl-D-aspartate-receptors (NMDA-Rs). Together, these results suggest a novel mechanism through which rTMS could modulate functional network connectivity by the preferential potentiation of specific subsets of synapses, e.g., excitatory synapses on proximal dendrites of neurons.

Kategorie: Lecture

Vortrag 22

Titel:Modulation of fgfr1/fgf2 trafficking in human glioma cells

Autoren: Irschick R.(1),Ramberger M.(2),Ecker J.(1),Trivik F.(1),Hausott B.(1),Marvaldi L.(1),Guo Q.(1),Youssef M.(1),Claus P.(3),Klimaschewski L.(1),

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Abstract:
Fibroblast growth factor receptors (FGFRs) and their ligands (FGFs) are key regulators during development, regeneration and tumorigenesis. Ligand binding is followed by endocytosis of the receptor/ligand complex and activation of intracellular signaling cascades. In this study, we analyzed FGFR1 and FGF2 trafficking in human glioma cells (U373 and T98G) and possible consequences of inhibition of Sprouty2, a negative feedback inhibitor of receptor tyrosine kinases, on trafficking and cellular proliferation. Following treatment of FGFR1-overexpressing glioma cells with labeled FGF2, internalization of receptor/ligand complexes was blocked by the endocytosis inhibitor methyl-beta-cyclodextrin (MbCD). MbCD-treatment also diminished translocation of exogeneously added FGF2 to the nucleus. FGF2-uptake was decreased slightly by dp12, a polysaccharide blocking ligand binding to heparan sulfate groups located on the cell surface. Both, FGFR1 and FGF2, colocalized with transferrin, suggesting that not only the receptor is recycled back to the cell surface, but also the ligand as indicated by analysis of total internal reflection (TIRF) microscopy. The recycling inhibitor monensin reduced colocalization with transferrin, too. Downregulation of Sprouty2 resulted in increased FGF2/FGFR1 recycling and enhanced cellular proliferation as revealed by flow cytometry analysis of EdU-incorporated cells. The FGFR-inhibitor PD173074 strongly inhibited proliferation of U373 cells, while inhibition of MEK/ERK did not reduce proliferation suggesting that PI3K/Akt signaling downstream of FGFR is mainly responsible for glioma growth in this cell line. In conclusion, modulation of receptor tyrosine kinase and ligand trafficking may result in novel treatment strategies to reduce receptor tyrosine kinase dependent cell proliferation and tumor growth.

Kategorie: Lecture

Vortrag 23

Titel:Mechanisms of adducin-dependent regulation of desmosomal adhesion

Autoren: Rötzer V.(1),Breit A.(2),Waschke J.(1),Spindler V.(1),

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Abstract:
Adducin is a protein organizing the cortical actin lattice underlying the plasma membrane. Previously, we have shown that antibody fractions of patients suffering from the blistering skin disease pemphigus vulgaris (PV-IgG) lead to rapid phosphorylation of adducin which represents a protective pathway to limit loss of cell cohesion. Here, we investigated the steps leading to adducin phosphorylation and the mechanisms by which adducin promotes intercellular adhesion. Binding of PV-IgG to human keratinocytes induced a rapid and transient increase in intracellular Ca2+, which was necessary for adducin phosphorylation at Ser726. Furthermore, Ser726 phosphorylation was dependent on protein kinase C (PKC) activation. Because PV-IgG targets the desmosomal adhesion molecules desmoglein (Dsg) 3 and Dsg1, we investigated the distribution of Dsg3 at the membrane with regard to adducin. Phosphorylated but not phosphorylation-deficient adducin prevented fragmentation of Dsg3 immunostaining in response to pemphigus autoantibodies and blunted loss of intercellular adhesion. Furthermore, adducin silencing induced a reduction of Dsg3 staining at the membrane whereas the distribution of other adhesion molecules such as E-cadherin was unaffected. Finally, fluorescence recovery after photobleaching (FRAP) experiments indicated that adducin primarily regulates Dsg3 membrane incorporation and/or lateral motility. These experiments provide novel insights into pemphigus-autoantibody-induced loss of cell cohesion and identify adducin as mechanistic link in actin dependent desmosome regulation.

Kategorie: Lecture

Vortrag 24

Titel:Live-imaging of adipose tissue inflammation identifies a new source of adipose tissue macrophages

Autoren: Gericke M.(1),Haase J.(1),Weyer U.(1),Braune J.(1),Immig K.(1),Klöting N.(2),Blüher M.(3),Eilers J.(4),Bechmann I.(1),

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Abstract:
Obesity is associated with low-grade inflammation of adipose tissue (AT) and increase of AT macrophages (ATMs) is linked to the onset type 2 diabetes. Here, we used three different models of mouse obesity and human samples to study the origin of ATMs in obesity. We show that besides monocyte recruitment from the blood stream, focal sites of inflammation around dying adipocytes, so-called crown-like structures (CLS), exhibit a microenvironment for macrophage proliferation. Upon feeding mice with a high fat diet (HFD), we found a time-dependent increase of ATM proliferation using histochemistry and flow cytometry. Interestingly, proliferating ATMs show no increase in marker proteins for classical activation (M1), such as CD11c or MHC II, but an increase in marker proteins for alternative activation (M2), such as CD206 and CD301. In line, stimulation with TH2 cytokines, such as IL-4, also increases ATM proliferation ex vivo. Further, live-imaging of AT explants from obese mice revealed that macrophages emigrate out of the CLS. In humans, we confirmed the increased expression of proliferation markers of CD68-positive macrophages in CLS and demonstrate a higher Ki67 mRNA expression in AT from obese and diabetic patients (n=239). Thus, local proliferation contributes to the increase of ATMs in obesity. Finally, our data identify CLS as the primary site of ATM proliferation. This work was supported by the DFG-SFB 1052 “obesity mechanisms” and the Helmholtz alliance “Imaging and Curing Environmental Metabolic Disease”.

Kategorie: Lecture

Vortrag 25

Titel:Control of apical-basal polarity in drosophila epithelia and neural stem cells

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Abstract:
The conserved scaffolding protein PAR-3 (Bazooka, Baz in Drosophila) functions on top of a hierarchy regulating the assembly of complexes which control apical-basal polarity in epithelia. In particular its interaction with atypical protein kinase C (aPKC), PAR-6 and the RhoGTPase Cdc42 has been shown to be crucial for the establishment of cell polarity. We and others have shown that phosphorylation of Baz/PAR-3 by aPKC within the C-terminal half of the protein triggers a dynamic composition of apical complexes. Thereby, the adaptor protein Stardust is activated for the stabilization of the Crumbs, which determines the apical domain. A second prerequisite for a stable Crumbs/Sdt interaction is functional PAR-6, although the particular mechanism underlying this phenomenon is described controversially. In Drosophila, a second region within Baz (PDZ2-3) has been found to interact directly with aPKC (Wodarz et al. 2000), raising the possibility that the interaction between Baz/PAR-3 and aPKC is mediated by two or more regions of the Baz protein. We now report the identification of additional phosphorylation sites for aPKC in Baz/PAR-3 PDZ2 and 3. Strikingly, phosphorylation of Baz PDZ2-3 by aPKC is essential for the initial establishment of epithelial polarity in the early embryonic epidermis but not in mature epithelia. Moreover we investigated the impact of Baz phosphorylation on aPKC kinase activity regulating asymmetric division of neural stem cells. Finally we come up with a model how PAR-6 contributes to the stabilization of the Baz-Sdt and Crumbs-Stardust complexes, thereby controlling crucial steps during the establishment and maintenance of apical-basal polarity.

Kategorie: Lecture

Vortrag 26

Titel:Modified planar cell movements lead to ancestral gastrulation in the mammalian embryo

Autoren:Stankova V.(1),Tsikolia N.(1),Viebahn C.(1),

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Abstract:
Animal gastrulation specifies the embryonic axes and induces epithelio-mesenchymal transition (EMT), the first major change in cell shape after fertilization; the ‘milieu intérieur’ is thus created in disparate topographical arrangements such as the circular blastopore of amphibians, the straight primitive streak of higher amniotes (birds and mammals) or, indeed, intermediate gastrulation forms of recent primitive amniotes (reptiles). As planar cell movements are known to be essential for establishing specific forms prior to, and during, gastrulation including EMT, we set out to modify mammalian gastrulation topography by interfering selectively with pre-gastrulation planar cell movements using rabbit blastocyst cultures and chemical inhibition of a Rho kinase (ROCK), a key factor in the planar cell polarity (PCP) pathway. Time-lapse videomicroscopy, high-resolution gene expression analysis and electron microscopy after ROCK inhibition using Y-27632 show normal formation and specification of the dorsal organizer but a dose-dependent bilateral displacement of EMT, giving the prospective primitive streak circular, arch-like, or intermediate forms similar to the ones known in amphibian, fish and reptiles, respectively. Our results reveal a critical role of the PCP-ROCK pathway during primitive streak formation in the mammalian embryo and support the idea that a temporal shift and limited adjustment of PCP-dependent cell movements may have driven the evolution of gastrulation forms.

Kategorie: Lecture

Vortrag 27

Titel:Epithelial flow into the optic cup facilitated by suppression of bmp drives eye morphogenesis

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Abstract:
The bi-layered vertebrate optic vesicles are formed by the bilateral evagination of the late prosencephalon, a process that in teleosts is driven by single cell migration. The transition of the oval optic vesicle to a hemispheric bi-layered optic cup involves major morphological transformations. In the classical view, the lens-averted epithelium of the optic vesicle differentiates into the retinal pigmented epithelium (RPE), while the lens facing epithelium gives rise to the neuroretina, which is subsequently bending around the developing lens. This neuroepithelial bending is driven by the basal constriction of lens facing retinal progenitor cells (RPC), which ultimately reduces the space an individual RPC is demanding. However, at the same time we find a 4.7 fold increase of the basal surface area. We show that the lens averted epithelium in fact functions as the cell reservoir for the forming neuroretina. Epithelial flow from the lens-averted into the lens-facing domain is driving the transformation from optic vesicle to optic cup. We show that the neuroretinal flow is modulated by BMP activity. Expression of BMP in retinal progenitor cells results in the disruption of neuro-epithelial flow during optic cup formation. This inhibition leads to a persisting neuroretina in the domain of the RPE and ultimately results in coloboma.

Kategorie: Lecture

Vortrag 28

Titel:Interaction between the meninges and the cortical neuroepithelium control gliogenesis during forebrain development

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Abstract:
Many organs develop by defined signaling events that depend on the timed interaction between epithial and mesenchymal tissues (kidney or tooth development for example). The development of the nervous system and that of the cortical neuroepithelium in particular, however, have rather been viewed as intrinsic and self regulatory. This view has been challenged by the analysis of Foxc1 mutant lines, which show a lateral expansion of the cortical neuroepithelium and consequently a delayed onset of neurogenesis. The important point is that Foxc1 is selectively expressed in the developing meninges that cover the cortical neuroepithelium. We have employed a co-culture system that allowed us to assess the cell biological consequences of the interaction between meningeal cells and cortical neural stem and progentor cells (NSCs). Surprisingly, we recorded an increase in gliogenesis rather than in neurogenesis as we had expected. We could biochemically identify three novel factors that appear to drive NSCs out of the cell cycle and promotes theier astroglial fate. Therefore we think that the meninges represent a source for extracellular signaling cues that are important for cortical development.

Kategorie: Lecture

Vortrag 29

Titel:Phenotyping e14.5 mouse embryos with high resolution episcopic microscopy (hrem)

Autoren: Weninger W.(1),Wilson R.(2),Geyer S.(1),Rose J.(1),Mohun T.(2),

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Abstract:
This presentation will show first results from employing HREM for phenotyping embryos of 30 mouse strains that produce prenatally lethal homozygous (-/-) offsprings. The embryos were produced in the scope of the Deciphering the Mechanisms of Developmental Disorders (DMDD) project, which is embedded in the International Mouse Phenotpying Consortium (IMPC). Three embryos of each line were harvested on embryonic day 14.5 and embedded in resin dyed with eosin and sectioned on a microtome. During sectioning, 2 000 to 4 000 digital images of the subsequently exposed block faces were captured. The images were virtually stacked to become volume data with voxel sizes of 3micronx3micronx3micron. First results of these phenotyping efforts will be briefly shown. They clearly demonstrate that HREM is capable of detecting subtle, but embryonically or perinatally lethal defects that will be definitively missed by all alternative 3D imaging techniques. Thus, the output of our presentation is threefold: Firstly it contributes to characterising the function of the gene outknocked in each of the 30 -/- strains; secondly it demonstrates the range of defects which are expected to be diagnosed in DMDD embryos; and thirdly it recommends HREM “the” tool for phenotyping embryos of strains producing embryonically lethal -/- individuals.

Kategorie: Lecture

Vortrag 30

Titel:Plasticity-related gene 5 expression promotes spine formation in hippocampal neurons

Autoren: Bräuer A.(1),Stoenica L.(1),Strauss U.(1),Coiro P.(1),

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Abstract:
The transmembrane proteins Plasticity-related gene 3 and -5 (PRG3, -5) increase filopodia formation in various cell lines, independently of Cdc42. However, information on PRG5 effects during neuronal development is sparse. Here, we present several lines of evidence for an involvement of PRG5 in genesis and stabilization of dendritic spines: first, PRG5 was strongly expressed during mouse brain development from embryonic day 14 (E14), peaked around the time of birth and remained stable at least until early adult stages (i.e. P30). Second, on a sub-cellular level, PRG5 expression shifted from an equal distribution along all neurites towards accumulation at dendrites during hippocampal development in vitro. Third, overexpression of PRG5 in immature hippocampal neurons induced formation of spine-like structures ahead of time. Proper amino acid sequences in the extracellular domains (D1 – D3) of PRG5 were a prerequisite for trafficking and induction of spine-like structures, as shown by mutation analysis. Forth, at stages when spines are present, knockdown of PRG5 reduced number but not length of protrusions. This was accompanied by a decrease in number of excitatory synapses and, consequently, by a reduction of mEPSC frequencies whereas mEPSC amplitudes remained similar. In turn, overexpressing PRG5 in mature neurons not only increased Homer-positive spine numbers, but also augmented spine head diameters. Mechanistically, membrane lipid-protein overlays suggested that PRG5 interacts with Phosphoinositolsphosphates (PIP’s), phospholipids involved in dendritic spine formation. Taken together, our data propose that PRG5 promotes spine formation.

Kategorie: Lecture

Vortrag 31

Titel:Molecular and functional analysis of a novel aqp4 isoforms in the cochlea

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Abstract:
The expression of aquaporin-4 (AQP4) in the epithelial supporting cells of the cochlear duct is crucial for hearing function. It has been hypothesized that AQP4 is involved in the intracellular osmotic water equilibration of the supporting cells during sensory transduction. In this study we analyzed (i) the anchoring mechanism, (ii) the expression pattern of different AQP4 isoforms (iii) and the functional water permeability of cochlear supporting cells. Immunohistochemical analysis revealed the co-localization of AQP4 and members of the dystrophin-associated protein complex (DAPC) in the cochlea in analogy to the muscle tissue, retina and cerebellum. However, until now AQP4 could never be identified in supporting cells of the sensory domain. Using an antibody generated in our lab specifically against the N-terminal epitope, AQP4 could be also immunolocalized in the supporting cells, which are in direct contact to excitable hair cells. The expression of this new AQP4 isoform in the cochlea could be confirmed by 3'RACE-PCR and sequencing. However, the novel isoform is not anchored via the DAPC and not clustered to orthogonal arrays of particles as revealed by freeze-fracture analysis. At the functional level the newly described AQP4 isoform exhibit a high degree of transmembrane water permeability.

Kategorie: Lecture

Vortrag 32

Titel:Deficiency of carcinoembryonic antigen-related cell adhesion molecule-1 (ceacam1) leads to formation of atherosclerotic lesions

Autoren: Ghavampour S.(1),Bömmel H.(1),Niedermeier N.(2),Benndorf R.(3),Ergün S.(1),

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Abstract:
Ceacam1 plays an important role in vascular hemostasis by regulating endothelial cell proliferation and survival. However, Ceacam1-deficiany (Cc1−/−) has no obvious effect on the early vascular development except increased vascular leakiness. Thus, we investigated whether Cc1−/− induces vascular lesions in atherogenic-prone aortae. Histological analysis revealed formation of aortic plaque-like lesions in Cc1−/− aortae accompanied with impaired endothelial integrity. Immunohistochemical analysis indicated inflammatory infiltration of monocyte and macrophages in the aortic wall of Cc1−/− mice. In vitro studies showed increased leukocyte adhesion to aortic wall of Cc1−/− mice, mediated in part by elevated level of vascular cell adhesion molecule. This effect is apparently mediated by endothelial cells, as adhesion of monocytes to cultured Cc1−/− myocardial endothelial (Myend) cells was also elevated compared to the WT Myend cells which express Ceacam1 at a high level endogenously. In this system, treatment of WT Myend cells with anti-Ceacam1 antibodies increases the effect of VEGF in monocyte-endothelial adhesion suggesting a cross-talk between the Ceacam1 and VEGFR-2 signaling pathways. Myend cells of Cc1−/− mice displayed a significantly higher VEGFR-2, but reduced eNOS level. Furthermore, Ceacam1 seems to directly interact with eNOS. Ceacam1 loss is associated with translocation of eNOS from cell membrane to Golgi-apparatus. The increased NADPH oxidase activity and plasma 8-isoprostane levels indicate oxidative stress in Cc1−/− aortae. Finally, Ceacam1 expression is up-regulated in endothelial cell covering the plaque area of ApoE-/- aorta. Taken together, our data identify Ceacam1 as relevant factor regulating the endothelial barrier and protecting the macrovessels against development of atherosclerotic lesions.

Kategorie: Lecture

Vortrag 33

Titel:Desmoglein-2 interaction is crucial for cardiomyocyte cohesion and function

Autoren: Wölfel A.(1),Schinner C.(1),Spindler V.(1),Vielmuth F.(1),Arnold E.(1),Waschke J.(1),

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Abstract:
Aims: We determined the contribution of the desmosomal cadherin desmoglein-2 to cell-cell-cohesion in cardiomyocytes. In the intercalated disc providing mechanical strength and electrical communication between adjacent cardiomyocytes, desmoglein-2 is closely associated with N-cadherin from adherens junctions and gap junctions. Methods and Results: We studied cell-cell-contacts between HL-1 cardiomyocytes by immunostaining of desmoglein-2 and N-cadherin to label area composita. Cohesion was measured using a novel liberase-based dissociation-assay. L-tryptophan interferring with the tryptophan-swap required for cadherin transinteraction caused irregular desmoglein-2 condensation and weakened cell-cell-cohesion, whereas phenylalanine had no effect. Since L-tryptophan did not affect N-cadherin localization and its effects were blocked by a desmoglein-specific tandem peptide, L-tryptophan appears to primarily interfere with desmoglein-2 distribution. Similarly, calcium-depletion and specific impairment of desmoglein-2 interaction by desmoglein-2 knockdown, a desmoglein-specific single peptide or antibody-competition reduced cardiomyocyte cohesion. L-tryptophane and single peptide induced ultrastructural disruption of junctions. Desmoglein-2 interaction was strengthened by desmoglein-2 overexpression. Certain but not all desmoglein-2 mutations associated with arrhythmogenic cardiomyopathy reduced cell-cell-cohesion indicating that not all desmoglein-2 mutations may contribute arrhythmogenic cardiomyopathy pathogenesis by this mechanism. Functional analyses at the organ level revealed an inefficient response to adrenergic stimulation in L-tryptophan-challenged murine Langendorff hearts paralleled by dyslocation of connexin 43 and beta1-adrenergic receptor. Conclusion(s): Our data demonstrate that desmoglein-2 plays a critical role in cardiomyocyte cohesion and function, especially in response to adrenergic stimulation as revealed in ex vivo preparations on the organ level.

Kategorie: Lecture

Vortrag 34

Titel:Direct inhibition of desmoglein 3 binding is not sufficient to induce loss of cell cohesion in keratinocytes as revealed by atomic force microscopy

Autoren: Vielmuth F.(1),Waschke J.(1),Spindler V.(1),

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Abstract:
Pemphigus vulgaris (PV) is a severe autoimmune disease in which autoantibodies against the desmosomal adhesion molecules desmoglein (Dsg) 1 and Dsg3 cause blister formation in the epidermis and the epithelium of mucous membranes. Two mechanisms are discussed to be required for loss of cell cohesion finally leading to blister formation: (I) Direct inhibition of Dsg interaction by autoantibodies binding to the extracellular domains and (II) intracellular signaling events which are altered in response to antibody binding. Here we used atomic force microscopy (AFM) to perform Dsg3 adhesion measurements on the surface of living keratinocytes to investigate the contribution of direct inhibition and signaling to loss of cell cohesion after treatment with Dsg3-specific autoantibodies. Dsg3 binding was drastically reduced after 15 and 30min of antibody exposition and the residual binding events demonstrated reduced binding forces. We next correlated these data with an important signaling event in PV, i.e. activation of p38MAPK. Interestingly, direct inhibition was partially blocked by inhibition of p38MAPK only whereas loss of cell-cell-adhesion was abrogated at the same time points. This demonstrates that p38MAPK signaling prevents loss of cell cohesion although Dsg3 binding is blocked. Furthermore, inhibiting lipid-raft-dependent Dsg3 internalization via methyl-ß-cyclodextrin (ß-MCD) also fully prevented loss of cell cohesion but did not reduce direct inhibition of Dsg3 binding. Taken together, these results indicate that inhibition of Dsg3 binding is not sufficient to cause loss of cell cohesion but rather alters signaling events which in turn induce cell dissociation.

Kategorie: Lecture

Vortrag 35

Titel:Calcineurin signalling in the thick ascending limb of the kidney

Autoren:Mutig K.(1),Borschewski A.(1),Dathe C.(1),Willnow T.(2),Bachmann S.(1),

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Abstract:
The furosemide-sensitive renal Na+-K+-2Cl--cotransporter (NKCC2) of the thick ascending limb (TAL) of the kidney is essential for the urinary concentration and renal electrolyte handling. NKCC2 activity is modulated by the balance between phosphorylation and dephosphorylation reactions. With-No-Lysine kinases interact with the homologous SPS-related proline/alanine-rich kinase and oxidative stress responsive kinase to provide the activating phosphorylation of the transporter. Little is known about phosphatases involved in its dephosphorylation and deactivation. Here we identify NKCC2 as a substrate of calcineurin and show that calcineurin inhibition using cyclosporine promotes NKCC2 function. To further characterize the molecular pathway involved in NKCC2 dephosphorylation we have evaluated SORLA (sorting-protein-related receptor with A-type repeats) knockout mice with nearly complete absence of phosphorylated NKCC2. We establish SORLA as trafficking factor that reduces the apical abundance of calcineurin in TAL thus facilitating NKCC2 phosphorylation. This study elucidates the molecular basis for calcineurin signalling along the TAL. Our results thus have substantial clinical implications for immunosuppressive therapy using calcineurin inhibitors since hypertension and electrolyte disorders often limit their therapeutic benefit.

Kategorie: Lecture

Vortrag 36

Titel:Arcuate nucleus pomc neurons control cannabinoid-induced feeding

Autoren:Koch M.(1),Kim J.(2),Varela L.(2),Kim J.(2),Hernandez F.(2),Bechmann I.(3),Simonds S.(4),Cowley M.(5),Dietrich M.(2),Diano S.(2),Horvath T.(2),

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Abstract:
Arcuate nucleus Agouti-related peptide (AgRP)-expressing neurons, when activated, rapidly induce feeding. On the other hand, activity of neighboring pro-opiomelanocortin (POMC) cells promote gradual onset of satiety. Reactive oxygen species (ROS) emerged as an inverse regulator of AgRP and POMC neurons, in which cellular ROS levels positively correlate with increased satiety and POMC tone and decreased AgRP activity. We asked whether cannabinoid receptor 1 (CB1R)-controlled feeding is also paralleled by altered ROS levels and neuronal activity of AgRP and POMC neurons. Here we show that chemical promotion of CB1R activity leads to decreased ROS levels and elevated activity of AgRP neurons and increased feeding. Strikingly, CB1R activation elevated ROS production and neuronal activity of POMC cells. This paradoxical increase in POMC activity was crucial for CB1R-induced feeding, because Designer Receptors Exclusively Activated by Designer Drugs (DREADD)-mediated inhibition of POMC neurons blocked CB1R-triggered food intake. The Pomc gene encodes both the anorexigenic peptide, alpha-melanocyte-stimulating hormone (alpha-MSH, and the orexigenic peptide, beta-endorphin. CB1R activation lead to selective increase in beta-endorphin but not in alpha-MSH in the hypothalamus, and, administration of the opioid receptor antagonist naloxone, blocked CB1R-induced feeding. Taken together, these results unmasked a previously unsuspected role of POMC neurons in promotion of feeding by cannabinoids.

Kategorie: Lecture

Vortrag 37

Titel:Tumor necrosis factor-alpha mediated denervation-induced homeostatic synaptic plasticity of dentate granule cells in entorhino-hippocampal slice cultures requires synaptopodin

Autoren:Becker D.(1),Lenz M.(1),Strehl A.(1),Zahn N.(1),Deller T.(1),Vlachos A.(1),

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Abstract:
Immune mediators affecting neural plasticity play a role in the course and pathogenesis of many neurological diseases. In the present study, we used the entorhinal denervation in vitro model to assess the role of Tumor necrosis factor-alpha (TNFa) in denervation-induced synaptic plasticity and tested whether TNFa could act through the regulation of Synaptopodin. This appeared to be a possibility, since our recent work showed that the actin-regulating protein Synaptopodin plays a crucial role in denervation-induced synaptic plasticity. Our results disclose that astrocytic TNFa mediates the ability of neurons to maintain a compensatory, i.e., homeostatic increase in excitatory synaptic strength following partial deafferentation. Furthermore, pharmacologic and genetic approaches revealed that TNFa induces changes in Synaptopodin-cluster properties, which appear to be required for homeostatic synaptic plasticity to occur. Taken together, we propose that an important downstream target of TNFa signaling is Synaptopodin, which could link this inflammatory cytokine at the molecular level to denervation-induced synaptic plasticity (supported by DFG).

Kategorie: Lecture

Vortrag 38

Titel:Pancortin-3 enhances substrate adhesion and focal contact-formation in podocytes and lung epithelial cells via wnt-signalling

Autoren: Koch M.(1),Bauer K.(2),Tamm E.(2),

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Abstract:
Purpose: Pancortins are glycoproteins of the olfactomedin family, which are encoded from a single gene. By alternative splicing, pancortins 1-4 are produced that share a middle part B with two different variations at the N-terminal (A1 or A2) and C-terminal (C1 or C2) sides. Pancortin-3, which is constitutively expressed in podocytes of the rat kidney (Kondo et al., JASN 2000) is a secreted variant that contains a C-terminal olfactomedin domain. As other olfactomedin proteins are involved in cell-cell and/or cell-matrix adhesion, we hypothesized that pancortin-3 might play a similar role in the glomerulus of the kidney and other epithelial tissues. Methods: To test our hypothesis, we developed an eukaryotic expression system and purified recombinant pancortin-3 by chromatography. Culture plates were coated with pancortin-3 to test its effects on substrate adhesion of podocytes and lung epithelial cells. Different signalling pathways were analyzed by real-time RT-PCR and western blotting. Results: Pancortin-3 significantly increases substrate adhesion of murine podocytes and human H441 cells to fibronectin, collagens I and IV, and laminin I, but has alone no effects on cell adhesion. The adhesion-promoting effects of pancortin-3 appear to be mediated by focal contact formation as they were blocked by adding RGD-peptides. Inhibitors of Wnt-signalling, such as sFRP-1 and DKK1 blocked the effects of pancortin-3 on substrate adhesion, and the formation of focal contacts and actin stress fibers. Conclusion: Pancortin-3 might contribute to cell-matrix adhesion of podocytes in vivo, an effect that is likely mediated by Wnt-signalling.

Kategorie: Lecture

Vortrag 39

Titel:Integration of martinotti cells into dis-/inhibitory cortical circuits

Autoren: Witte M.(1),

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Abstract:
GABA releasing interneurons play a crucial role in the information processing within the primary somatosensory (barrel) cortex. Martinotti cells, a well-defined subclass of GABAergic interneurons, are integrated in the network of local pyramidal cells, thereby having direct influence on the barrel cortex output structures. Martinotti cells receive strong and temporally precise inhibition during active whisking, which could be partially attributed to upstream vasoactive intestinal polypeptide (VIP)-expressing interneurons. To study the neocortical origin of inhibitory inputs to Martinotti cells we used a combination of whole-cell patch clamp and local photolysis of caged glutamate in acute brain slices to identify local neocortical areas, at a layer- and column-specific resolution, responsible for inhibition of Martinotti cells of layer (L) II/III and LV. Martinotti cells of LII/III obtain strong and focused (>50%) inhibitory inputs from their home layer in their home column. In contrast, Martinotti cells of LV receive extensive inhibitory inputs from LVa and LVb and a reliable portion from LII/III of the home column. By crossing PV (parvalbumin)cre- or VIPcre-expressing lines with GIN-mice, and stereotaxic injection of floxed ChR2-mCherry viral vectors we could show that the populations of VIP- and PV-expressing interneurons project to LII/III and LV Martinotti cells. To verify our optogenetic approach, we perform paired patch-clamp recordings from Martinotti cells and their presynaptically connected inhibitory interneuron in triple transgenic mice. Based on their electrophysiological characterization and morphological appearance we could clearly identify the connection between VIP- or PV-expressing interneurons and Martinotti cells in the barrel cortex in a layer-specific manner.

Kategorie: Lecture

Vortrag 40

Titel:High-resolution microscopy of the axon initial segment and the cisternal organelle in retinal ganglion cells in vivo

Autoren: Engelhardt M.(1),Schlüter A.(1),Rossberger S.(2),Gutzmann A.(1),Schultz C.(1),

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Abstract:
The cisternal organelle (CO) is a putative Ca2+-storage and release compartment comprised of stacks of smooth endoplasmic reticulum. The CO is exclusively localized to the axon initial segment (AIS) of a subpopulation of CNS neurons. Our own recent studies have indicated that the AIS is dynamically regulated during development and matures in an activity-depended manner in the visual system, however, it remains unknown how this axonal plasticity is regulated. We now hypothesize that the CO plays a role during AIS plasticity. Furthermore, we present first evidence showing that the morphological maturation of the CO is subject to activity-dependent dynamic regulation in the visual system. We apply high-resolution microscopy techniques and biochemical assays to address the precise subcellular structure and localization of the CO as well as its molecular composition in AIS of retinal ganglion cell (RGC) axons. Data are obtained from wildtype mice immunostained for synaptopodin, a key regulatory protein of the CO. Interestingly, only a subset of RGCs have a CO, some of which possess multiple synaptopodin-positive CO clusters, the functional relevance of which is currently under investigation. Morphometric analysis after scanning laser confocal microscopy and a combination of Structured Illumination and Single Molecule Localization microscopy shows that (1) the AIS of RGCs is significantly longer than of any other neuronal cell class analyzed to date, (2) a periodic spatial distribution of scaffolding proteins extending from the axonal surface towards the inner cytoskeleton is evident, and (3) the cluster size of synaptopodin/CO is subject to activity-dependent regulation.

Kategorie: Lecture

Vortrag 41

Titel:Aromatase inhibition influences synaptic correlates of spatial learning

Autoren: Vierk R.(1),Freitag S.(2),Muhia M.(2),Kneussel M.(2),Rune G.(3),

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Abstract:
Inhibitors of aromatase, the final enzyme of estradiol synthesis, are suspected of inducing memory deficits in women. In previous experiments, we found impairment of long-term potentiation (LTP) in female mice that had been treated with letrozole, a potent aromatase inhibitor. The impairment was progressive, started after six hours of treatment and after 1 week of treatment theta-burst stimulation failed to induce LTP. Impairment of LTP was followed by loss on hippocampal spine synapses. Interestingly, these effects were not found in male animals. In order to find out whether the cellular effects after inhibition of estrogen synthesis in females may also have adverse effects on the behavioral level, we tested male and female mice in the Morris water maze (MWM) task to examine a putative influence of letrozole on hippocampal-dependent spatial-based learning and memory. We applied letrozole at a dose similar to the dosis, which is used in the therapy of breast cancer. At this dose we found no changes in synaptic potentiation in males, but a significant reduction in LTP in female mice. In a pilot study of MWM spatial learning, letrozole injection resulted in altered learning in females, an effect that was not observed in males.

Kategorie: Lecture

Vortrag 42

Titel:S-scam/magi-2 is essential for synapse formation and maintenance

Autoren: Wittenmayer N.(1),Böning A.(1),Viotti J.(1),Dresbach T.(1),

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Abstract:
Synaptic scaffolding molecule (SSCAM)/ membrane-associated guanylate kinase inverted-2 (MAGI-2) was originally characterized as a scaffold protein interacting with N-methyl-D-aspartate (NMDA) receptors at excitatory synapses. Furthermore it was shown that it is an essential synaptic scaffolding molecule for the GluA2-containing maintenance pool of AMPA receptors. Despite its function at mature synapses, little is currently known for the function of S-SCAM/MAGI-2 during early synaptogenesis. Using an RNAi based knockdown approach, we found that S-SCAM/MAGI-2 regulates synapse formation and maintenance. Knockdown of all three S-SCAM/MAGI-2 isoforms in rat hippocampal neurons during early synaptogenesis leads to a dramatic reduction of synapses on these cells. Restoring S-SCAM/MAGI-2 levels with alpha, beta or gamma S-SCAM/MAGI-2, rescues the phenotype. Electrophysiological data show that synaptic transmission is severely reduced. Synapses that are still formed on S-SCAM/MAGI-2 knockdown neurons display mismatched pre- and postsynaptic terminals. Our data suggest that the postsynaptic scaffolding protein S-SCAM/MAGI-2 is crucial for synapse formation and maintenance.

Kategorie: Lecture

Vortrag 43

Titel:Cortical network dysfunctions in response to hyperstimulated nrg1/erbb4 signaling

Autoren: Schwab M.(1),Unterbarnscheidt T.(2),Soto Bernardini M.(2),Brzozka M.(3),Dibaj P.(4),Zhang M.(5),Willig K.(6),Rossner M.(3),Ehrenreich H.(7),Zhang W.(5),Agarwal A.(8),Nave K.(4),

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Abstract:
Cortical network dysfunctions in response to hyperstimulated NRG1/ErbB4 signaling Neuregulin (NRG) 1 is a growth and differentiation factor with an epidermal growth factor (EGF)-like signaling domain and serves as a ligand for receptor tyrosine kinases of the ErbB family. NRG1/ErbB signaling regulates multiple aspects of nervous system development and synaptic plasticity in the mature brain. Variants of the human NRG1 and ErbB4 genes are risk factors for schizophrenia. Increased NRG1 expression and ErbB4 hyperphosphorylation was found in postmortem brains of schizophrenia patients, suggesting that NRG1/ErbB4 hyperstimulation represents a possible pathomechanisms in schizophrenia. We have shown that ‚global' neuronal overexpression of NRG1 in the brain of ‚conventional' transgenic mice leads to brain abnormalities with relevance for schizophrenia, including altered spine growth and ventricular enlargement. To study NRG1/ErbB4 hyperstimulation in a more selective in vivo model, we have generated ‚conditional' transgenic mice, which allow Cre recombinase-mediated NRG1 overexpression in glutamatergic projection neurons. Compared to ‚global' overexpression, cortex-restricted NRG1 overexpression ‚rescues' weight loss, ventricular enlargement, and defects in sensorimotor gating observed in ‚conventional' transgenic mice. This suggests brain area-specific NRG1 functions and indicates a modulatory role of NRG1 in subcortical networks. Preliminary findings suggest that a prenatal exposure to hyperstimulated NRG1 signaling has more profound consequences on behavioral functions compared to postnatal exposure, consistent with the neurodevelopmental hypothesis of schizophrenia. These studies will help to identify brain deficits caused by NRG1/ErbB4 hyperstimulation with relevance for schizophrenia, and could provide novel targets for future treatment strategies of schizophrenia.

Kategorie: Lecture

Vortrag 44

Titel:Looking at the transcripional basis of daily adaptation in retina and photoreceptor cells

Autoren: Wolloscheck T.(1),Kunst S.(1),Trunsch P.(1),Hölter P.(1),Kelleher D.(1),Wengert A.(1),Weyer V.(2),Sticht C.(3),Wolfrum U.(4),Iuvone M.(5),Tosini G.(6),Spessert R.(1),

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Abstract:
The retina - and in particular photoreceptor cells - adapt to daily changes in the environment. In the present study daily adaptation of the retina as a whole and of microdissected photoreceptor cells were investigated at the level of gene expression. With regard to the regulation of adaptation, 24-h changes in gene expression were found to be promoted by a circadian clock, light input, melatonin signaling/melatonin receptor type I and dopamine signaling/dopamine D4 receptors, depending on the gene concerned. With regard to genes constituting the basis of daily adaptation, it became evident that genes that act as master regulators of energy metabolism (Esrrbeta, Pgc-1alpha) and modulators of visual signaling (Kcnv2) are involved. The data for this suggests that daily adaptation of gene expression complies with daily changes in metabolic and functional demands and - on a long-term basis – in this way may contribute to the survival of photoreceptor cells. This study was supported by grants from the Naturwissenschaftlich-Medizinischen Forschungszentrum (NMFZ) of the University of Mainz.

Kategorie: Lecture

Vortrag 45

Titel:The clock gene period1 drives daytime-dependent fluctuations in spatial working memory performance: mechanism of action.

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Abstract:
It is well documented across different animal models and learning paradigms that memory processes (acquisition, consolidation and retrieval) are influenced by daytime, and modulated by a circadian clock. However, the mechanism(s) behind the temporal gating of learning and memory remain unknown. Our recent findings demonstrate that signaling and epigenetic modifications not only cycle across day and nighttime in mouse hippocampus, but, that this rhythmic molecular characteristic is dependent and influenced by the clockwork component PERIOD1 (PER1) (1,2). Importantly, we also demonstrated that the PER1-dependent temporal fluctuations in hippocampal signaling reflects on hippocampus-dependent memory processes, as in long-term improvements of spatial working memory performance (2). One of the identified PER1-dependent molecular rhythms is the phosphorylation/activation of the transcription factor CREB (cyclic adenosine monophosphate responsive element binding protein), essential for long-term memory persistence (2). Here we report that PER1 is necessary for day/night differences in learning-induced CREB activation, likewise to the presented daytime-dependent pharmacological activation of this ‘memory molecule’ in hippocampal slices. Furthermore, we elucidate the molecular mechanism underlying the PER1-dependent regulation of CREB phosphorylation, by dissecting memory relevant molecular pathways that signal to CREB in the hippocampus. Our data open a novel molecular facet in the role of clock genes as modulators of spatial working memory performance, an essential adaptive behavior for the survival of animals within their natural habitat. 1. Jilg et al., Hippocampus 2010, Mar;20(3):377-88. 2. Rawashdeh et al., Hippocampus 2014, Jun;24(6):712-23.

Kategorie: Lecture

Vortrag 46

Titel:Seeded beta-amyloidosis in long-term hippocampal slice cultures

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Abstract:
A major pathological hallmark of Alzheimer's disease is the aggregation and deposition of amyloid-beta (Aß) peptides in the brain. According to the amyloid cascade hypothesis the accumulation of Aß is an early and central event. Thus, great effort is made to study the mechanisms of Aß aggregation and pathogenicity in vitro and in vivo. Here, we combined the advantages of both approaches and established a long-term hippocampal slice culture (HSC) model for ß-amyloidosis. HSCs were prepared from either wildtype or amyloid precursor protein (APP) transgenic mouse pups. Initially, the cultures were treated once with brain extract (BE) from wildtype mice or from different Abeta-depositing APP transgenic mice and then incubated for 9 weeks. The culture medium was continuously supplemented with different synthetic Aß species. Aß deposition was monitored by electron microscopy and immunohistochemistry. Aß deposition in the cultures was observed only with combined treatment of BE from APP transgenic mice and synthetic Aß in the culture media. Aß deposits were detected after 4 weeks and progressed thereafter. The source of the transgenic BE and the synthetic Aß species used determined the morphotypes of the Aß deposits. The induced Aß deposition was partially Congo red-positive and revealed the birefringence under polarized light. Aß-immunogold labeled amyloid fibers were observed at ultrastructural level. This HSC model is a new tool to study ß-amyloidosis. It combines the accessibility of a controlled environment with the advantages of a living system. Supported by BMBF (BH: 031A198B, MJ: 031A198A).

Kategorie: Lecture

Vortrag 47

Titel:The novel notch ligand egfl7 governs adult neurogenesis in vivo

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Abstract:
In neurobiology the dogma on the unchangeability of the adult mammalian brain and its inability to give rise to new neurons has been challenged since the early nineties. Generally, it is now accepted that neurogenesis occurs in the adult brain and originates from neural stem cells (NSCs) that reside in stem cell niches such as the subventricular zones (SVZ) in the lateral walls of the lateral ventricles. A central molecular pathway regulating NSCs and adult neurogenesis is the Notch signaling cascade. Previously, we identified the secreted epidermal growth factor-like protein 7 (EGFL7) as a novel non-canonical Notch ligand promoting neuronal differentiation of NSCs in vitro that acts by competing with canonical Notch ligands of the Jagged type (Schmidt et al., Nat Cell Biol, 2009). In order to determine whether or not EGFL7 regulates NSCs in vivo we explored an EGFL7 knock-out mouse model and performed cerebroÂ¬ventricular injection studies of adenoviruses encoding for EGFL7 into the lateral ventricle of adult mice. Further, we performed expression analyses and quantitative mass spectrometry (SILAC) in order to understand the molecular mechanism behind EGFL7â€™s impact on NSCs. Last, we analyzed the population of newborn neurons in the olfactoric bulb and correlated the data with mouse behavior. The combination of in vivo models and comprehensive signaling studies revealed that EGFL7 exerts a profound and Notch-dependent effect on the architecture of the NSC niche in the SVZ. In conclusion, EGFL7 governs adult neurogenesis in vivo and is an important player in the regeneration of the adult brain.

Kategorie: Lecture

Vortrag 48

Titel:Neuroinflammation triggers peripheral cell recruitment in a multiple sclerosis animal model

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Abstract:
Anti-myelin immunity is commonly considered to drive multiple sclerosis lesion development, yet the initial trigger for peripheral immune cell recruitment remains elusive. One of the recently proposed factors for initiating immune cell invasion is neuroinflammation (i.e. oligodendrocyte death alongside with reactive gliosis). To specifically test our hypothesis that brain intrinsic inflammation triggers peripheral cell recruitment, we induced neuroinflammatory foci by systemic cuprizone intoxication and investigated the recruitment of anti-myelin specific immune cells into the white and grey matter forebrain under autoimmune conditions. Cuprizone-induced neuroinflammation triggers strong microglia and astrocyte activation, which result in demyelination and significant axonal damage. Conditions favoring autoimmunity, for instance the presence of myelin-reactive T cells, evoke the recruitment of peripheral immune cells into neuroinflammed brain regions. These foci are characterized by the accumulation of T cells within perivascular spaces, a disturbed integrity of the glia limitans perivascularis and the penetration of T cells into the brain parenchyma. Results of adoptive transfer experiments and FACS analyses suggest that myelin components in secondary lymphatic tissues boost anti-central nervous system immunity. Furthermore, qtPCR studies indicate that brain intrinsic chemokine expression with concomitant endothelial activation are pivotal for peripheral immune cell recruitment. In conclusion, we provide experimental proof for the assumption that a primary cytodegeneration (possibly focused on the oligodendrocyte–myelin complex) is the initial event during multiple sclerosis lesion formation. By releasing highly antigenic constituents, neuroinflammation secondarily promotes an autoimmune and inflammatory response in predisposed hosts.

Kategorie: Lecture