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Abstract Nr.:1

Titel: Laminar activity patterns in the human hippocampus and entorhinal cortex related to novelty detection and episodic encoding

Autoren: Emrah Düzel, Magdeburg (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic I
Abstract Nr.:2

Titel: Genetics of the glutamatergic synapse and the functional neuroanatomy of human memory

Autoren: Björn Schott, Magdeburg (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic I
Abstract Nr.:3

Titel: Fear memory circuits in amygdala and hippocampus: role(s) of GABAergic interneurons

Autoren: Oliver Stork, Magdeburg (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic I
Abstract Nr.:4

Titel: Transcriptional control of hippocampal neurogenesis

Autoren: Stefan Britsch, Ulm (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic I
Abstract Nr.:5

Titel: Testing the behavioural relevance of GABAergic interneurons in cortical circuits

Autoren: Peer Wulf, Kiel (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic I
Abstract Nr.:6

Titel:Characterization of tyrosine hydroxylase mrna-expressing neurons in the dopamine depleted mouse striatum

Autoren: Tasler M.(1),Lepzien R.(1),Schmitt O.(1),Wree A.(1),Haas S.(1),

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Abstract:
Transferring the 6-hydroxydopamine (6-OHDA) rat model of Parkinson's disease to mice is of great interest. However, in contrast to rats a high quantity of TH-containing neurons can be observed in the mouse striatum after dopamine depletion. Darmopil et al. (2008) suggests that these neurons emerge from a phenotypic shift of neurons, which are already present in the striatum prior 6-OHDA-injection. Therefore, our current study aimed to further characterize the phenotype of TH-mRNA expressing neurons in the striatum by using a transgenic mouse producing GFP under the control of the TH-promoter (TH-GFP+). Mice received a unilateral injection of 6-OHDA into the medial forebrain bundle. Successful lesions were evaluated by apomorphine-induced rotations. Animals were perfused 3 days or 3 months postlesion. TH-GFP+ neurons appeared in the striatum as early as 3 days after lesion. By 3 month post lesion TH-GFP+ neurons were present throughout the entire striatum. Though, the vast majority of these cells were detected in the rostral part of the striatum. In comparison to other studies we also did not find any newly generated cells containing doublecortin. Less than 1% of TH-GFP+ neurons expressed calretinin, identifying this subpopulation as interneurons. Comparing lesioned and non-lesioned hemispheres, there were no obvious differences in the quantity of calretinin expressing cells. TH-GFP+ neurons were never immunoreactive for choline acetyltransferase (ChAT). In our study only 10% of GFP+ neurons were co-localized with calbindin, indicating them as projection neurons. Further characterization of these TH-GFP+ neurons in the striatum is currently performed by using these transgenic mice.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:7

Titel:Differences in social behavior, prepulse inhibition, dopaminergic and serotonergic hippocampal fiber density of CPB-K mice compared to BALB/cJ mice

Autoren: Nullmeier S.(1),Panther P.(2),Kröber A.(1),Wolf R.(3),Schwegler H.(1),

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Abstract:
Patients suffering from schizophrenia show disturbances in social, cognitive and sensorimotor functions. Also, morphological alterations in cortical and subcortical areas, like reduced hippocampal AMPA- NMDA-, 5-HT2-receptor densities and increased 5-HT1-receptor densities are known. Schizophrenia is discussed to be caused by a dysregulation of neuronal transmitter systems which will be ameliorated by antipsychotics. The two inbred mouse strains, CPB-K and BALB/cJ display considerable differences in cognitive function and prepulse inhibition (PPI), a stable marker of sensorimotor gating. Further, CPB-K mice exhibit lower NMDA-, AMPA- and increased 5-HT-receptor densities in the hippocampus as compared to BALB/cJ mice. We investigated both mouse strains in social behavior and PPI. Also, immunocytochemical investigations of dopaminergic and serotonergic parameters were carried out. CPB-K mice, compared to BALB/cJ, showed: (1) a reduced traveling distance and number of contacts in social interaction test, (2) a reduction of PPI, that was not improved after four-week treatment with clozapine, (3) differences in the number of serotonergic neurons and volume of raphe nuclei and a lower serotonergic fiber density in the ventral and dorsal hippocampal CA1 and CA3, (4) no alterations in dopaminergic subregions of substantia nigra and ventral tegmental area, but a higher dopaminergic fiber density in dorsal hippocampus, ventral hippocampal CA1 and gyrus dentatus and (5) no differences in the amygdala. CPB-K mice compared to BALB/cJ may serve as an important model to understand the interaction of the serotonergic and dopaminergic system and their impact on sensorimotor gating and cognitive function as related to neuropsychiatric disorders like schizophrenia.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:8

Titel:The role of bcl11b/ctip2 in the adult hippocampus

Autoren: Simon R.(1),Baumann L.(1),Fischer J.(1),Seigfried F.(1),Andratschke J.(1),Schwegler H.(2),Britsch S.(1),

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Abstract:
The hippocampus, in particular the dentate gyrus is one of the two brain regions where adult neurogenesis occurs. The ability to generate new neurons throughout life provides a basis for generating and storing new memory, an important hippocampal function. Previously we have shown that the transcription factor Bcl11b/Ctip2 plays an import role in postnatal development of the dentate gyrus. In a dual phase-specific function Bcl11b/Ctip2 regulates the progenitor cell compartment by feedback control as well as granule cell differentiation leading to impaired spatial learning and memory behavior in mutants (EMBO J, 2012, 13: 2922-2936). Bcl11b/Ctip2 expression occurs also throughout adulthood raising the question of its function in the adult organ. Generating an inducible mouse line using the Tet-off system under the control of the CaMKIIa promoter we demonstrate for the first time a specific role for Bcl11b/Ctip2 in the maintenance of adult hippocampal functions. Selective ablation of Bcl11b/Ctip2 in adult hippocampal neurons causes mossy fiber as well as synapse instability leading to impaired spatial learning. Taken together our data presented here establish an essential role for the transcription factor in the maintenance of adult hippocampal function.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:9

Titel:Mice calorie restricted for 74 weeks show better spatial learning than ad lib-fed mice

Autoren: Kuhla A.(1),Lange S.(2),Holzmann C.(3),Vollmar B.(1),Wree A.(2),

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Abstract:
Age-related impairments of cognitive functions are a well known phenomenon. Caloric restriction (CR) is one of the most effective strategies to prolong life span in a variety of organisms and to prevent age-related diseases. Controversy exists as to whether 40% CR has no effect on, enhances or disrupts cognitive function during aging in mice.
In this study mice starting at the age of 4 weeks were caloric restricted for 4, 20 and 74 weeks. Caloric restricted mice received 60 % of food eaten by their ad libitum (AL) fed sisters, and all age-matched groups were behaviourally analyzed.
Following CR for 4 weeks, body weight was reduced on average by 27.4±0.3%, for 20 weeks by 32.7±0.2%, and for 74 weeks by 38.2±0.4%. The rotarod/accelerod, testing motor coordination, revealed no significant differences between AL and CR mice in any age-group. Analysis of mice by open field test and elevated plus maze test showed lower locomotor activity and increased anxiety in the 74 weeks CR group. Most importantly, in the Morris water maze, measuring spatial memory, the 74 weeks CR mice significantly performed better than the age-matched AL mice concerning the escape latency and the time in goal quadrant.
We observed profound effects on the behaviour of CR mice mainly following 74 weeks food restriction. However, locomotor activity and anxiety and spatial memory were differently and contrarily influenced by caloric restriction. Thus, caloric restriction must be reconsidered with respect to the final benefit for the elderly people.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:10

Titel:Mice, melatonin and the maintenance of chronotypes

Autoren: Wicht H.(1),Korf H.(1),Ekhart D.(1),Pfeffer M.(1),

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Abstract:
Humans come in different chronotypes - a few of us are very early birds (\"morning type\"), some others extreme night-owls (\"evening type\"), but most of us are \"intermediates\". There is a large number of other behavioral, social, physiological and health-related issues that covary together with the individual chronotype.

The biological machinery that maintains the chronotype and the daily rhythms in general (the so-called circadian system) is frequently investigated in inbred mice. It is not known, however, whether these (nocturnal) animals also come in different chronotypes. If they did, they would offer the opportunity to study the establishment, maintenance and corollaries of the chronotype in all (molecular and genetic) detail.

We have analyzed the general locomotor activity in different inbred mouse-strains and did indeed find different, strain-specific chronotypes. Some strains accomplish most of their \"locomotor workout\" already early in the night, while others take their time and extend their activities well into the morning. Thus, there seems to be a genetic contribution to the chronotypic behavior. We have also investigated the influence of the melatoninergic system (melatonin is one of the main effector hormones of the circadian system) on the chronotype. Mice from strains that do have defects in this system (be it the lack of melatonin or its receptors) reproduce their daily rhythms (and thus: their chronotype) with less accuracy than those with an intact system, even though the general (averaged over several days) early or late chronotype remained largely unaffected.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:11

Titel:Polarization and positioning of cortical neurons critically depend on cofilin

Autoren: Chai X.(1),Fan l.(2),Shao H.(2),Zhao S.(1),Frotscher M.(1),

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Abstract:
Postmitotic neurons migrate from their birthplace, the ventricular zone, to their final destinations in the cortical plate, thereby forming the laminated neocortical organization.. During migration, cortical neurons show a bipolar morphology with a long, thick leading process and a short, thin trailing process. This characteristic polarization is important for the directed neuronal migration process. The motility of migrating neurons is based on cytoskeletal dynamics that requires constant remodelling of the actin and microtubule cytoskeleton. Cofilin, an actin-depolymerizing protein, is known to be involved in the reorganization of the cytoskeleton by severing actin filaments. The activitiy of cofilin is reversibly regulated by phosphorylation and dephosphorylation at Ser3, with the phosphorylated form being inactive. Conditional knockout mice showed that loss of n-cofilin impaired radial neuronal migration, resulting in the lack of proper cortical lamination. To this end, we have studied the roles of n-cofilin and its phosphorylation at Serine3 by using in utero electroporation to transfect postmitotic neurons in the cerebral cortex of mouse embryos with different constructs of n-cofilin including knockdown of n-cofilin and point mutations at serine3. We found that overexpression of n-cofilin as well as n-cofilin knockdown and point mutations at Ser3 all interfered with the proper polarization and migration of cortical neurons, pointing to a critical role of n-cofilin in these processes.
(Supported by the DFG: FR 620-12/1)

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:12

Titel:Wiring up sensory neocortex under conditions of massive cellular disorganization: does the thalamus find its ectopic target cells in reeler mutant mice?

Autoren: Wagener R.(1),Staiger J.(1),

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Abstract:
Thalamic projections are highly ordered. In the rodent brain, axons from the ventral posteromedial thalamic nucleus mainly project to layer IV of the primary somatosensory cortex. The molecular mechanisms enabling thalamocortical axons to reach their target cells are poorly understood.
The reeler mouse is a mutant which shows a severely impaired cortical organization. Cells with different laminar fates are mixed up and become distributed all over the cortical thickness. This is also true for cells that are fated for layer IV. These cells cluster in a columnar compartment building barrel equivalents, which can be functionally activated by behavioral tasks (Wagener et al., 2010). This raises the question if layer IV cells receive a thalamic input even in their ectopic position. We reconstructed the barrel equivalent, as well as the distribution of thalamic fibers within the columnar equivalent. Moreover, we examined the composition of activated cells within the reeler columnar equivalent concerning their affiliation to excitatory and subgroups of inhibitory cells.
We found that the thalamic axons form asymmetric patches, which strictly correspond to asymmetric barrel equivalents being smeared out over the cortical plate. In the disorganized reeler column the same composition of excitatory and inhibitory cells participate in the activation of neuronal networks as in the wild type column. Thus, thalamic axons are capable to establish highly ordered connections with their ectopic (layer IV) target cells. Therefore, we suggest that cell-autonomous molecular cues and not gradients of attractive and repulsive factors are responsible for correct wiring in the thalamocortical pathway.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:13

Titel:Unravelling cerebellar pathways with high temporal precision targeting motor and extensive sensory and parietal networks

Autoren: Sultan F.(1),

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Abstract:
Increasing evidence has implicated the cerebellum in providing forward models of motor plants predicting the sensory consequences of actions. Assuming that cerebellar input to the cerebral cortex contributes to the cerebro-cortical processing by adding forward model signals, we would expect to find projections emphasising motor and sensory cortical areas. However, this expectation is only partially met by studies of cerebello – cerebral connections. Here we show that by electrically stimulating the cerebellar output and imaging responses with functional magnetic resonance imaging, evoked blood oxygen level-dependant activity is observed not only in the classical cerebellar projection target, the primary motor cortex, but also in a number of additional areas in insular, parietal and occipital cortex, including sensory cortical representations. Further probing of the responses reveals a projection system that has been optimized to mediate fast and temporarily precise information. In conclusion, both the topography of the stimulation effects and its emphasis on temporal precision are in full accordance with the concept of cerebellar forward model information modulating cerebro-cortical processing.

Kategorie: Lecture

Rubrik: Main Topic I
Abstract Nr.:14

Titel:Plexin a2 and neuropilin 2 signalling are involved in the axonal guidance of cranial nerves

Autoren: Haque(1),Pu(1),Huang(1),

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Abstract:
Plexin A2 and Neuropilin 2 signalling have been shown to be involved in the axonal guidance of the spinal motor nerve and cranial nerves. Here we intend to investigate whether these signals are involved in the development of cranial nerves in the head trunk transitional region from which glossopharyngeal, vagal, accessory and hypoglossal nerves originate. For this purpose, shRNA-EGFP constructs affecting the Plexin A2 and Neuropilin 2 pathway were electroporated into the neural tube of two days old chick embryos. After two days of reincubation, the treated embryos were analyzed by in situ hybridization and immunohistochemistry. We observed that somata of dorsolaterally migrating motor neurons translocated into the periphery along the accessory nerve root if the Plexin A2 signalling was affected. Affection of this signalling also led to defasciculation of hypoglossal axons. Furthermore, interruption of Neuropilin 2 signalling caused defasciculation of vagal and accessory axons. Our results suggest that the Plexin A2 and Neuropilin 2 signalling are involved in the axonal guidance of cranial nerves in the head trunk transitional region.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:15

Titel:Desmoglein 2 is less important for cell cohesion in keratinocytes compared to intestinal epithelial cells

Autoren: Hartlieb E.(1),Vigh B.(1),Spindler V.(1),Waschke J.(1),

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Abstract:
Desmoglein (Dsg) 2 is the most widespread isoform of the desmosomal cadherin protein family, of which four desmoglein (Dsg1-4) and three desmocollin (Dsc1-3) isoforms are expressed in keratinocytes. In the blistering skin disease pemphigus vulgaris (PV), Dsg3 is a target of autoantibodies indicating a central role for Dsg3 in keratinocyte cohesion. In contrast, for Dsg2 the role for keratinocyte cohesion has not been defined yet. We demonstrated the importance of Dsg2 for intestinal epithelial cells by incubation of Caco2 cells with a monoclonal Dsg2 antibody (Dsg2 mAb) which led to a significant loss of cell cohesion as detected in a dissociation assay. However, Dsg2 mAb, in contrast to AK23, a pathogenic PV antibody targeting Dsg3, did not reduce cell-cell adhesion in a human keratinocyte cell line (HaCaT) and a squamous carcinoma cell line (SCC9). To confirm that both antibodies are potent to bind their target protein we detected both antibodies´ heavy chains by Western blot analysis. Additionally we quantified binding events of recombinant Dsg molecules in a cell free system using atomic force microscopy (AFM). Both antibodies led to a decrease in the number of binding events of their corresponding target protein. In contrast to another colorectal adenocarcinoma cell line (HT-29), siRNA-mediated silencing of Dsg2 in HaCaT cells reduced cell cohesion only under conditions of increased shear. These results indicate that Dsg2 contributes differently to cell cohesion dependent on the expression pattern of desmosomal cadherin family isoforms.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:16

Titel:Pemphigus and the actin cytoskeleton – role of adducin and rhoa

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

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Abstract:
Previous data demonstrated that the loss of keratinocyte cohesion by desmoglein (Dsg) autoantibodies in the blistering skin disease pemphigus vulgaris (PV-IgG) is paralleled by pronounced reorganization of the cortical actin belt and can be blocked by Rho-GTPase activation. Here, we investigated the role of adducin, a protein known to organize the cortical actin lattice, in Rho-GTPase-mediated strengthening of keratinocyte cohesion. Adducin silencing reduced Dsg3 protein levels and decreased intercellular adhesion of human keratinocytes in dispase-based dissociation assays, which was accompanied by disruption of cortical actin. Cell dissociation caused by AK23, a pathogenic a-Dsg3 antibody derived from a pemphigus mouse model, was blocked by E. coli cytotoxic necrotizing factor (CNF)-1-induced activation of RhoA, Rac-1 and Cdc42 as well as by specific RhoA activation via the Y. pseudotuberculosis toxin CNF-y. However, under conditions of adducin silencing the protective effect of both CNF-1 and CNF-y was abrogated. Similar results were obtained when an adducin mutant was expressed which was phosphorylation-deficient at Serin726. This residue is important for regulation of adducin activity and rapidly is phosphorylated following incubation with CNF-1 and CNF-y, but also with AK23. These experiments demonstrate that adducin is necessary for proper intercellular adhesion and that the protective effect of RhoA activation against pemphigus autoantibody-mediated cell dissociation is dependent on adducin phosphorylation. Furthermore, because AK23 also induced adducin phosphorylation at the same residue under this condition, it is conceivable that Rho-GTPase activation is capable to enhance an endogenous protective pathway to rescue keratinocyte cohesion.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:17

Titel:Sorting protein-related receptor sorla facilitates degradation of calcineurin and thereby promotes phosphorylation of renal na+-k+-2cl- cotransporter

Autoren: Mutig K.(1),Borschewski A.(1),Willnow T.(2),Dathe C.(1),Paliege A.(1),Ferreri N.(3),Bachmann S.(1),

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Abstract:
Background/Purpose:
Activity of the Na+-K+-2Cl- cotransporter (NKCC2) of the thick ascending limb (TAL) is dependent on its N-terminal phosphorylation. Sorting protein-related receptor SORLA was shown to facilitate this process, but the underlying mechanisms are not fully understood. We hypothesized that SORLA may interfere with kinases or phosphatases relevant for NKCC2 phosphorylation.

Methods:
We have studied the regulation of the proline/alanine-rich kinase (SPAK), oxidative stress responsive kinase 1 (OSR1), and calcineurin phosphatase A (CnA) in wildtype (WT) and SORLA-deficient (SORLA-/-) kidneys using immunoblotting, co-immuno¬precipitation (co-IP), and confocal microscopy. Functional analyses included SPAK/OSR1-knockdown in cultured cells and application of the calcineurin inhibitor, cyclosporin A (CsA), in vivo and in cell culture.

Results:
SPAK, OSR1 and the calcineurin isoform CnAß were co-localized with NKCC2 in mouse and rat TAL. Knockdown of SPAK/OSR1 in cultured rat TAL cells decreased-, while CsA treatment increased NKCC2 phosphorylation, confirming the functional relevance of these kinases and the phosphatase for the transporter. SORLA-deficiency was associated with near-absent NKCC2 phosphorylation (-84%), unchanged abundance and distribution of SPAK and OSR1 kinases, but increased abundance of the CnA isoform in the apical compartment of TAL (+201%). Short term administration of CsA to SORLA-/- mice restored their decreased NKCC2 phosphorylation levels, suggesting that CnAß was responsible for the impaired phosphorylation of the transporter upon SORLA-disruption. Co-IPs from rat kidney revealed interactions of CnA with both NKCC2 and SORLA.

Conclusion:
Our results suggest that SORLA participates in calcineurin degradation in TAL and thus facilitates NKCC2 phosphorylation

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:18

Titel:Nrf2 loss promotes liver cancer after ddc administration to mice

Autoren: Wruck C.(1),Streetz K.(2),Fragoulis A.(3),Schenkel J.(3),Herzog M.(3),Pufe T.(3),

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Abstract:
Liver cancer is the third leading cause of cancer death. The functional role of oxidative stress in cancer pathogenesis has long been a hotly debated topic. Nrf2 is, the major regulator implicated in the endogenous defence system against oxidative stress. Therefore, Nrf2-knockout and hepatic Keap1-knockout mice, which have a hepatocyte specific overactive Nrf2, were feed on 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) containing diet and were examined for hepatic tumorigenesis at seven months. Thus, DDC enhanced liver cancer in mice lacking Nrf2 may be due to their vulnerability to oxidative stress.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:19

Titel:„SP-H“, a putative new immunological and surface-regulatory lung surfactant protein – tissue localization, functionally analysis and 3D structure

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Abstract:
Surfactant proteins and their multifunctional properties (SP) are well known from human lung. These proteins assist during the formation of a monolayer of surface-active phospholipids at the liquid-air interface of the alveolar lining, play a major role in lowering the surface tension of interfaces and have functions in the innate and adaptive immune system. During recent years it became obvious that SPs are also part of other tissues and fluids such as tear fluid, gingiva, saliva, the nasolacrimal system, and kidneys. In this work, computational chemistry and molecular-biological methods were combined to detect, localize and characterize a putative new surfactant protein for the first time, called SP-H. Assisted by a developed protein structure model, specific antibodies were obtained which allowed the detection of SP-H not only on mRNA but also on protein level. The localization of this protein in different human tissues, sequence based prediction tools for posttranslational modifications and molecular dynamic simulations reveal that SP-H has physicochemical properties similar to the already known surfactant proteins B and C. This includes also the possibility of interactions with lipid systems and with that, a potential surface-regulatory feature of SP-H. Moreover, real-time RT-PCR studies indicate possible immunological functions of SP-H. In conclusion, our results suggest SP-H to be new member of the surfactant protein family.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:20

Titel:The concentration of urea in tear liquid at patients with diabetes and keratoconjunctivitis sicca as possible consequence of an endothelial impairment

Autoren: Kolokowsky S.(1),Langguth F.(1),Kielstein H.(1),Jäger K.(1)

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Abstract:
The concentration of urea in tear liquid at patients with diabetes and keratoconjunctivitis sicca as possible consequence of an endothelial impairment

The enzymes for production of urea were expressed at the surface of the eyes. Thus far there is now other source of urea production known and a correlation between the amount of urea in tear liquid and other bodily fluid at healthy subjects could not establish.
We investigated the concentration of urea in tear and in aqueous fluid of diabetes patients with and without keratoconjunctivitis sicca compared to healthy subjects. To verify if increased concentration of urea in tear liquid is associated with altered kidney values we sampled tear liquid, aqueous liquid, blood and urine from 227 patients with diabetes and 84 healthy subjects.
Patients with diabetes and keratoconjunctivitis sicca had a higher concentration of urea in tear liquid than Patients without sicca and healthy subjects. Our researches shown, that the concentration of urea in tear liquid of patients with diabetes correlates with the concentration in the blood. Additionally there was a significant association between the concentration of urea in tear liquid and the kidney values.
It might be that microangiopathic changes of small vessels of the eyes makes the blood-tear- and blood- aqueous border permeable and porous. Urea of the blood could trespass into tear liquid. This could lead to an increase of the concentration of urea in tear liquid at Patients with diabetes and causes a keratoconjunctivitis sicca syndrome.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:21

Titel:Is the change in cartilage thickness in the femorotibial joint related to severity of contra-lateral radiographic knee status? -1-year data from the osteoarthritis initiative

Autoren: Cotofana S.(1),Wirth W.(2),Olivier B.(3),Eckstein F.(1),

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Abstract:
Purpose: Knee osteoarthritis is associated with clinical and structural disease progression, particularly in radiographically advanced stages. Being able to predict fast structural progression is crucial for setting up clinical trials that evaluate structure modifying therapy. We here investigate the impact of the radiographic status of the contra-lateral knee on annual femorotibial cartilage thickness loss.

Methods: We studied 837 participants (62.4±9yrs; 30±4.9kg/m²; 61.8% females) with definite early (Kellgren and Lawrence Grade [KLG] 2) and advanced (KLG3) radiographic knee osteoarthritis (ROA) from the Osteoarthiritis Initiative cohort between baseline and 1-year follow-up. Segmentation and thickness computation of the femorotibial cartilage was performed on MR images using proprietary software

Results: 219 KLG2 knees had no radiographic joint space narrowing (JSN) and 278 KLG2 knees had JSN. All 340 KLG3 knees had JSN. In KLG2 knees with JSN, those with severe contra-lateral ROA had significantly (p<0.001) greater cartilage loss (-221/20.1) (µm/SEM) than those without contra-lateral ROA (-142/8.4). The rate of change in those with severe contra-lateral radiographic change was similar to that in KLG 3 knees (-232/17.7) without contra-lateral ROA.

Discussion: In knees with early radiographic osteoarthritis (KLG2) but with JSN, contra-lateral radiographic status appears to be a potent predictor of subsequent cartilage loss. KLG2 knees with JSN and with (severe) contralateral radiographic osteoarthritis may provide a unique opportunity for recruitment in clinical trials as they are still at a relatively early disease stage, but nevertheless have a high likelihood of fast structural progression.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:22

Titel:Thigh muscle strength in knee osteoarthritis is strongly determined by pain but not by radiographic stage - data from the osteoarthritis initiative

Autoren: Ruhdorfer A.(1),Wirth W.(1),Hitzl W.(2),Eckstein F.(1),

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Abstract:
Reduced thigh muscle strength is commonly observed in knee osteoarthritis. However, whether this is a cause or consequence of the disease remains unclear. This study attempts to dissect whether reduced muscle strength is associated with pain or with radiographic disease stage.
3809 right knees (2201 women) from the Osteoarthritis Initiative (OAI; n=4674; http://www.oai-ucsf.edu/datarelease/) were selected for this cross-sectional, observational study. Isometric extensor and flexor muscle strength was measured at 60degree knee flexion (Good Strength Chair, Metitur Oy, Finland). Participants were stratified by WOMAC knee pain scores (range 0-20, 4 questions with a 5-point-maximum: 0=no pain; >=5=pain), and radiographic Kellgren-Lawrence-grades (KLGs0=no, n=1378; KLG1=minimal, n=698; KLG2=definite, n=1054; KLG3/4=advanced radiographic osteoarthritis, n=679). Different pain states were compared within each KLG-stratum, and painless limbs between KLG-strata (age-adjusted separate slopes ANCOVA model).
Extensor strength was significantly less in painful than in painless limbs (p<0.05) in either sex and across all radiographic stages: It was -9 (95%CI 1-18) to -17% (95%CI 12-23) in women and -11 (95%CI 3-20) to -14% (95%CI 5-23) in men. Similar results were observed for flexor strength. In painless limbs extensor and flexor strength did not significantly differ across radiographic KLG-strata (p=0.28/0.13 in women, p=0.47/0.63 in men).
Reduced muscle strength in knee osteoarthritis strongly depends on presence of pain but not radiographic disease stage. The findings suggest that the reduction in muscle strength more likely is a pain-related consequence of knee osteoarthritis than the cause of radiographic incidence or progression.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:23

Titel: Arteries of the arm - clinical aspects

Autoren: Claassen H.(1), Schmitt O.(2), Schulze M.(2), Wree A.(2),

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Abstract:
Variations of arteries of the upper limb are of great clinical impact. The following signs may indicate a variation: Pulsation of subcutaneous vessels, aggravating and repetitive pain, absence of radial and ulnar pulses, differences in blood pressure in the range of 40 mm Hg. Here, we report about variabilities of upper limb arteries which were observed during 4 dissection courses in the Department of Anatomy (University of Rostock).
Classical ramification of axillary artery is rare (<10-40%). Some or all branches can derive from a common trunk. Variant axillary arteries often are combined with variances of the brachial plexus. During brachial plexus anaesthesia, local anaesthetic has to overcome a greater distance if the fork of the median nerve and the median nerve itself have moved behind axillary artery or variant branches of this artery. Ulnar artery can take a superficial course (2%) and can be mistaken for a vein during venous blood sampling. Radial artery can take a high origin (4%) from axillary or brachial arteries. Remnants of the phylogenetic old superficial brachial artery are responsible for this phenomenon. Variations of radial artery have to be taken into account when this vessel is used for percutaneous coronary intervention. Furthermore, the superficial course of ulnar and radial arteries is meaningful for forearm flaps in reconstructive surgery. A large patent comitans nervi mediani artery, called median artery (7%), can cause carpal tunnel syndrome, and, furthermore, anterior interosseous nerve or pronator syndrome if it passes through the proximal median nerve. Heredity seems to play a role in cases of a brother and a sister with absent radial pulse; here radial artery has changed its way from palmar to dorsal in the distal forearm.
In conclusion, arteries of the adult can have persisted on an embryonic stage and this could be responsible for the abundant diversity of arterial variations.

Kategorie: Lecture

Rubrik: Main Topic II
Abstract Nr.:24

Titel: Antigens in the food - candidates and their uptake

Autoren: Jean-Paul Lallès, Rennes (France)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic II
Abstract Nr.:25

Titel: Follow the traces of migrating immune cells

Autoren: Anja Hauser-Hankeln, Berlin (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic II
Abstract Nr.:26

Titel: The role of Interleukin-7 in the regulation of intestinal homeostasis

Autoren: Thomas Schüler, Magdeburg (Germany)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic II
Abstract Nr.:27

Titel: Meet the antigen in the lamina propria: Dendritic cells and lymphocytes

Autoren: Mick Bailey, Bristol (U.K.)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic II
Abstract Nr.:28

Titel: Allergens and the mucosa

Autoren: Risto Renkonen, Helsinki (Finland)

Abstract:
Gastredner, daher: Übersichtsrefrerat

Rubrik: Main Topic II
Abstract Nr.:29

Titel:Mas-related gene receptor d is expressed in the (inflamed) human and mouse intestine and is implicated in neuroimmune interaction during intestinal inflammation

Autoren: Avula L.(1),Buckinx R.(2),Pintelon I.(2),De Winter B.(3),Adriaensen D.(2),Salgado R.(4),Van Nassauw L.(5),Timmermans J.(2),

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Abstract:
We have previously shown that Mas-related gene receptor D (MrgD) is expressed de novo in the mouse intestine during (Schistosoma mansoni-induced) inflammation, specifically in sensory neurons and newly recruited mucosal mast cells (MMCs). We have also shown that, under the same condition, MrgD-deletion leads to increased MMC recruitment and sensory neuropeptide expression. Based on these results, we have now further explored the role(s) of MrgD in mast cell and sensory neuron-associated responses. Immunohistochemical stainings showed that MrgD-expressing MMCs and sensory neuropeptide-expressing nerve fibres in the lamina propria are in close proximity, adding support to the previously suggested Mrg receptors' involvement in mast cell-sensory neuron bidirectional communication. Using live cell imaging, we found that the MrgD ligand â-alanine, which is a putative neurotransmitter, evoked a Ca2+ influx in a subset of in vitro-derived mast cells expressing MrgD, suggesting that â-alanine could be a candidate mediator in the neuroimmune interactions. The direct activation of neuronal MrgD and the signal transduction mechanisms remain to be explored, but comparison of gastrointestinal motility between the healthy and S. mansoni-infected wild-type and MrgD-/- mice, did not reveal changes between the two groups, indicating that MrgD-induced neuronal changes would only influence the sensory pathways during intestinal inflammation. In parallel, we have identified that as in mouse, MrgD is expressed in neurons and mast cells in the human intestine, suggesting possible translational potential. Our findings justify the further exploration of MrgD as an experimental target in intestinal inflammatory pathologies, focusing on sensory perception and neuroimmune interactions.

Kategorie: Lecture

Rubrik: Main Topic II
Abstract Nr.:30

Titel:Role of host-defense peptides in innate immune defense at the ocular surface

Autoren: Garreis F.(1),Gottschalt M.(1),Jahn J.(2),Wild K.(1),Paulsen F.(1),

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Abstract:
The ocular surface including the lacrimal system and lids has evolved several defense mechanisms to prevent microbial invasion. Included among this armory are several host-defense peptides (HDPs). In this study the expression and regulation of human beta-defensins, psoriasin and S100 fused-type proteins Hornerin and Filaggrin-2 at the ocular surface were investigated. The expression of HDPs was systematically determined by RT-PCR, Western Blot and immunohistochemistry in tissues of the ocular surface from different body donors. In addition, tear fluid obtained from different healthy volunteers was examined by ELISA for its hBD-2, hBD-3 and psoriasin concentration. Regulation and inducibility of HDPs were studied in cultivated corneal and conjunctival epithelial cells after challenge with frequent ocular pathogens, proinflammatory cytokines as well as different exogenous stress factors. Our results revealed that hBD1, -2, -3 and -4 are constitutively expressed in conjunctiva and also partly in cornea. Psoriasin and hornerin are constitutively expressed in cornea, conjunctiva, nasolacrimal ducts and lacrimal gland. Healthy tissues of the ocular surface and human tears contain measurable amounts of hBD2 and -3 and in a much higher concentration psoriasin. Proinflammatory cytokines and different pathogen-associated molecular patterns induce the expression of hBD-2, hBD-3 and psoriasin in different intensity in cultivated cells. Our results expand the current knowledge of HDPs expression and their role in the innate immune defense at the ocular surface. These multifunctional molecules are being studied not only for their endogenous antimicrobial properties but also for their potential therapeutic effects.

Kategorie: Lecture

Rubrik: Main Topic II
Abstract Nr.:31

Titel:The mandibular ridge oral mucosa model of stromal influences on the endothelial tip cells

Autoren: Didilescu A.(1),Rusu M.(2),Pop F.(3),Manoiu V.(4),Jianu A.(5),Valcu M.(6),

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Abstract:
Sprouting angiogenesis is led by endothelial tip cells (ETCs). The aims of the present study were to evaluate by immunohistochemistry and transmission electron microscopy (TEM): 1. the morphological features of the oral mucosa ETCs, and 2. the immune and ultrastructural patterns of the stromal non-immune cells. Immune labeling was performed on bioptic samples obtained from six edentulous patients undergoing surgery for dental implants' placement; three normal samples were also collected from patients prior to the extraction of the third mandibular molar. Slides were prepared and immunostained with antibodies for CD34, CD117(c-kit), PDGFR-alpha, Mast Cell Tryptase, CD44, vimentin, CD45, CD105, alpha-SMA, FGF2, Ki67. Light microscopic examination revealed stromal cells of the reparatory and normal oral mucosa, with a fibroblastic appearance, positive for a CD34/CD44/CD45/CD105/PDGFR-alpha/vimentin immune phenotype, whilst the CD117/c-kit labeling led to a positive stromal reaction only in the reparatory mucosa. In TEM, non-immune stromal cells presenting particular ultrastructural features were identified as circulating fibrocytes (CFCs). Within the lamina propria CFCs were in close contact with ETCs. The relationship between ETCs and CFCs suggests a possible role played in maintenance and healing of oral mucosa by extensive processes of angiogenesis. Therefore, CFCs could be targeted by specific therapies, with pro- or anti-angiogenic purposes.

Grant sponsor(s): the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government; Grant number: POSDRU/89/1.5/S/60782.

Kategorie: Lecture

Rubrik: Main Topic II
Abstract Nr.:32

Titel:Sulforaphane has opposing effects on tnf-alpha stimulated and unstimulated synoviocytes

Autoren: Fragoulis A.(1),Tohidnezhad M.(1),Rosen C.(1),Pufe T.(1),Wruck C.(1),

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Abstract:
Introduction: Rheumatoid arthritis (RA) is characterized by progressive inflammation associated with rampantly proliferating synoviocytes and joint destruction due to oxidative stress. Recently, we described nuclear factor erythroid 2 related factor 2 (Nrf2) as a major requirement for limiting cartilage destruction. NF-kappaB and AP-1 are the main transcription factors triggering the inflammatory progression in RA. We used sulforaphane, an isothiocyanate, which is both an Nrf2 inducer and a NF-kappaB and AP-1 inhibitor.
Methods: Cultured synoviocytes were stimulated with sulforaphane (SFN) with or without TNF-alpha pre-treatment. NF-kappaB, AP-1, and Nrf2 activation was investigated via dual luciferase reporter gene assays. Matrix metalloproteinases (MMPs) were measured via zymography and luminex technique. Cytokine levels were detected using ELISA. Cell viability, apoptosis and caspase activity were studied. Cell proliferation was analysed by real-time cell analysis.
Results: SFN treatment decreased inflammation and proliferation dose-dependently in TNF-alpha-stimulated synoviocytes. SFN did not reduce MMP-3 and MMP-9 activity or expression significantly. Interestingly, we demonstrated that SFN has opposing effects on naïve and TNF-alpha-stimulated synoviocytes. In naïve cells, SFN activated the cytoprotective transcription factor Nrf2. In marked contrast to this, SFN induced apoptosis in TNF-alpha-pre-stimulated synoviocytes.
Conclusions: We were able to show that SFN treatment acts contrary on naïve and inflammatory synoviocytes. SFN induces the cytoprotective transcription factor Nrf2 in naïve synoviocytes, whereas it induces apoptosis in inflamed synoviocytes. These findings indicate that the use of sulforaphane might be considered as an adjunctive therapeutic strategy to combat inflammation, pannus formation, and cartilage destruction in RA.

Kategorie: Lecture

Rubrik: Main Topic II
Abstract Nr.:33

Titel:Blood-epididymis barrier: immunoregulatory cytokine tgfbeta modulates paracellular permeability in the epididymal epithelium

Autoren: Stammler,A.(1),Konrad,L.(2),Müller,D.(1),Middendorff,R.(1),

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Abstract:
The selective permeability of the epididymal epithelium is essential for controlling the milieu in the luminal liquid. The epithelial barrier shields the lumen of the epididymal duct from biological agents present in blood and lymph, protecting sperm from the immune system. Defective barrier function can disturb the balance of the epididymal milieu, which may result in infertility.
The interstitium of the epididymis contains high amounts of TGFbetas. The function of the TGFbetas in the epididymis has not been investigated so far. TGFbetas are important regulators of cell differentiation and immune response. They are also known to control the paracellular tightness of epithelial barriers in diverse organs.
We analyzed the effects of the three TGFbeta isoforms on the epididymal barrier in an in-vitro model. Cultured epididymal epithelial cells were treated with recombinant TGFbetas. Permeability was analyzed using trans-epithelial electrical resistance and tracer diffusion assays. We found a significant increase of permeability elicited by TGFbetas, especially TGFbeta3, within four to six hours of treatment. These effects could be completely abolished by TGFbeta receptor inhibition. In addition, we noted a possible implication of non-Smad-pathways. Preliminary data provided evidence for distinct effects of TGFbetas on the distribution of tight junctions.
Our data suggest that TGFbetas are important factors for the control of paracellular permeability in the epididymal duct, which might be part of the inflammatory response caused by bacterial infection.
Grants: DFG: KFO 181, Hessia: LOEWE-MIBIE

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:34

Titel:X-ray irradiation phase advances the molecular clockwork in subsidiary clocks

Autoren: Müller M.(1),Korf H.(1),

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Abstract:
The mammalian system is hierarchically organized with a master clock in the suprachiasmatic nuclei (SCN) of the hypothalamus and subsidiary clocks (peripheral oscillators) located in virtually all organs. Both central clock and peripheral oscillators contain a molecular clockwork whose center is a primary transcriptional/translational feedback loop comprising a positive limb with the activators BMAl1 and CLOCK and a negative limb with the repressors PER1-3 and CRY 1 and 2. Molecular clockworks in peripheral organs are not self-sustained, but depend on signals transmitted under SCN control. Here we investigated whether X-ray irradiation influences the molecular clockwork in subsidiary clocks. Organotypic slice cultures were prepared from liver (OLSC) and adrenal gland (OAEC) of transgenic Per2luc mice which express luciferase under control of the Per2 promoter and thus allow to monitor the rhythm in Per2 expression by bioluminometric real time recordings. OLSC and OAEC were cultured in a membrane-based liquid-air interface culturing system. Bioluminometric real time recordings showed that the circadian rhythm in Per2 expression persisted in OLSC and OAEC for up to 12 days in vitro. In samples irradiated with X-rays at doses of 10 Gy and 50 Gy the rhythmic expression of Per2 persisted with unchanged period length, but a dose of 50Gy phase-advanced the rhythm in Per2 expression by 6h in OLSC and by 4h in OAEC. These results show that X-ray irradiation directly affects the molecular clockwork in peripheral oscillators and extend results showing that radiation-induced DNA damage resets the circadian system in whole animals.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:35

Titel:Ste20-like kinase spak differentially regulates na-(k)-cl cotransporters along the distal nephron under the endocrine control of avp

Autoren: Bachmann S.(1), Saritas T.(2),McCormick J.(3),Ellison D.(3),Delpire E.(4),Mutig K.(1),

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Abstract:
The Na-K-2Cl cotransporter (NKCC2) of the thick ascending limb (TAL) and the Na-Cl cotransporter (NCC) of the distal convoluted tubule (DCT) are critical for renal salt handling. Activation of these transporters by vasopressin (AVP) includes their N-terminal phosphorylation. Little is currently known about the kinases that mediate this action of AVP. Two homologous Ste20-like kinases, SPAK and OSR1, can phosphorylate the cotransporters directly. In this process, full-length SPAK variant (FL-SPAK) and OSR1 interact with a truncated isoform, KS-SPAK, which has inhibitory effects. Here we have tested the hypothesis that SPAK is an essential component of the AVP stimulatory pathway.

Short- and long-term effects of desmopressin (dDAVP), a V2 receptor-specific agonist, on the kinases and transporters were evaluated in wild type and SPAK-deficient mice and in AVP-deficient rats.

SPAK variants displayed prominent regulatory changes along TAL and DCT along with activation of the cotransporters, whereas OSR1 was less involved. The KS- and FL-SPAK variants were modulated by AVP for their selective interaction with NKCC2 in control of its activation, whereas the phosphorylation of NCC was essentially governed by FL-SPAK alone.

In sum, our data specify how SPAK may serve as a hallmark kinase in modulating Na+ reabsorption along the distal nephron under the endocrine control of AVP.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:36

Titel:The podocyte cytoskeleton is responsive to estradiol

Autoren: Fester L.(1),Oh J.(2),Rinn C.(2),Rune G.(1),

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Abstract:
One of the most common causes of nephrotic syndromes in children is the Minimal-Change-Glomerulonephritis (MCGN). Typically, MCGN results in foot processes effacement of podocytes. Their plate-shaped flattening is presumed to induce an increase in albumin concentrations in the urine. Notably, MCGN often disappears as the children enter into puberty with the corresponding increase in peripheral hormone levels. This is particularly true in girls.
Podocytes express estrogen receptors both, estrogen receptor alpha and beta, suggesting that increasing levels of estradiol during puberty maintains morphological integrity of podocytes. This protective function could be mediated by stabilization of the podocyte cytoskeleton by estradiol, as evidenced in vitro by the increase in phosphorylation of cofilin, very similar to the effects of estradiol in neurons. Podocytes also express the enzyme aromatase, which converts testosterone into estradiol. We show that dissociated podocytes in fact synthesize estradiol in vitro, since considerable amounts of estradiol are detectable by radioimmunoassay in the supernatant. As it was shown that estrogen synthesis in cells other than those in gonads becomes stimulated during puberty, an autocrine mechanism could underlie decreasing frequency of MCGN at the onset of puberty.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.: 37

Titel:The suburothelial interstitial cells in rat -an immunohistochemical and ultrastructural study

Autoren: Rusu M.(1),Pop F.(2),Folescu R.(3),Manoiu S.(4),Didilescu A.(5),

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Abstract:
The suburothelium has received renewed interest because of its role in sensing bladder fullness. Various studies evaluated either suburothelial myofibroblasts, interstitial cells (SUICs), interstitial Cajal cells, or telocytes, leading to inconsistencies in terminology and difficulties in understanding the suburothelium structure. In order to elucidate these issues, the use of electron microscopy seems to be an ideal choice
The present study hypothesized that distinctive cell types participate in the suburothelial band structure, attempting to clarify the above mentioned inconsistencies. The bladder suburothelial interstitial cells were evaluated by immunohistochemistry (IHC) and transmission electron microscopy (TEM). Six Wistar rats were used. Desmin labeled the detrusor muscle, but not other different myoid structures of the bladder wall, which, in turn, were labeled by alpha-smooth muscle actin (alpha-SMA) antibodies. A distinctive myoid layer, alpha-SMA positive, was identified by IHC immediately beneath the urothelium.
A layered structure of the immediate suburothelial band was detected in TEM: (1) the inner suburothelial layer consisted of fibroblast-like cells (FLCs), equipped for matrix synthesis; (2) the middle suburothelial layer consisted by smooth muscle cells (SMCs) and suburothelial myoid interstitial Cajal cells (SUICCs); (3) the outer suburothelial layer consisted of interstitial cells (SUICs) building a distinctive network.
In conclusion, the suburothelial layer is built up by distinctive types of interstitial cells, but not myofibroblasts. The myoid layer, with SMCs and SUICCs, seems the best equipped for pacemaking and signaling. Noteworthy, the network of SUICs seems suitable for stromal signaling.

Kategorie: Lecture

Rubrik: Cell Biology
Abstract Nr.:38

Titel:A virtual correlative transmission electron microscope

Autoren: Voigt T.(1),

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Abstract:
In the long run the widespread use of slide scanners by pathologists requires an adaptation of teaching methods in histology and cytology which also points to these new possibilities of image processing and presentation via the internet. Accordingly we were looking for a tool with the possibility to teach microscopic anatomy, histology and cytology of tissue samples which independently of suppliers of microscopes is capable to combine image data from light and electron microscopes. With the example of a section through the villus of jejunum, we describe here how to process image data from light and electron microscopes in order to get one image-stack which allows a correlation of structures from the microscopic anatomic to the cytologic level. With commercially available image-presentation software which was adapted to our needs, we present here a platform which independently of microscope suppliers allows for the presentation of this new but also of older material.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:39

Titel:Selective functions for the star family proteins sam68, slm-1 and slm-2 in neural stem cells

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Abstract:
Neural stem cell (NSC) proliferation and differentiation are tightly controlled during embryonic development. Environmental, niche-derived signals activate or silence intracellular signaling cascades and so orchestrate NSC behaviour. We have recently identified the signal transduction and activation of RNA metabolism (STAR) protein Sam68 as cellular integrator in NSCs during mouse CNS development. Here, we systematically assessed the highly related STAR family proteins Sam68, Slm-1 and Slm-2 for their expression during forebrain development and cell biological function in NSCs. Each STAR family protein displayed a unique expression pattern in dividing NSCs as well as in postmitotic neurons in different forebrain regions. Functionally, overexpression of Sam68 and Slm-1 by nucleofection of cultured NSCs selectively increased NSC differentiation to the neuronal lineage, which was accompanied by increased cell-cycle exit and reduced neurosphere formation. In contrast, Slm-2 showed opposing activities as it promoted the maintenance of NSCs in a proliferative state. Differentiation and maturation of oligodendroctes was specifically promoted by Sam68. Biochemically, we identified that all three STAR family proteins engage the MAP kinase pathway. Increased STAR family protein levels reduced ERK phosphorylation in response to EGF. In contrast, Slm-2 selectively sustained MAP kinase signalling in response to FGF2. So all STAR proteins differentially affect NSCs despite engagement of the same signalling pathway. Our data emphasize the importance of STAR family proteins in NSC behaviour and we have identified distinct cell biological roles for each STAR family protein despite their high degree of homology at the molecular level.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:40

Titel:Identification of novel mechanisms involved in oligodendrocyte loss during early demyelination

Autoren: Clarner T.(1),Victor M.(1),Goldberg J.(1),Berger K.(1),Beyer C.(1),Kipp M.(1),

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Abstract:
Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system (CNS). Neuropathological evidence suggests that a primary oligodendrogliopathy triggers the inflammatory response in a subgroup of patients during MS lesion development. The induction of apoptotic responses in oligodendrocytes is accompanied by microglia accumulation and activation in MS and related animal models.
We recently showed that unfolded protein responses (UPR) are functionally involved in oligodendrocyte loss and that oligodendrocytes can initiate the microglial immune response by the release of the chemokine CXCL10 in vivo.
Here we demonstrate that disturbances in mitochondrial functions trigger the expression of UPR signalling molecules. Distinct subunits of the mitochondrial respiratory chain were inhibited in vitro and expression of UPR marker genes determined. We could show a stimulus dependent induction of CHOP, ATF3, ATF4 and Grp94 in two distinct oligodendroglial cell lines. Beyond that, we further characterized the role of the transcription factor CHOP for initiating apoptosis in cuprizone-induced demyelination. CHOP deficient mice were utilized for this part of the study. Our data highlight the role of mitochondrial functions and signalling for the initiation of UPR in oligodendrocytes. Further experiments will have to show the molecular link between mitochondrial dysfunction, triggering of UPR, expression of transcription factor CHOP and the release of chemotactic molecules by stressed oligodendrocytes.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:41

Titel:Quantitative, functional analysis of the astrocytic secretome

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Abstract:
The astrocytic secretome is vital for axon guidance, neurogenesis, and regeneration. We used in-depth SILAC-label based mass spectrometry for functional analysis of astrocyte secretion in vitro. For the first time, we provide precise quantitation of the extra-to-intracellular protein ratio of more than two thousand identified proteins, including many that were previously not known to be secreted. Functionally, the secretome of labelled forebrain astrocytes specifically changed within hours after adding unlabelled forebrain neurons vs. cerebellar hindbrain neurons. We describe an exhaustive set of specific patterns of protein up- and downregulation between control and neuron-exposed conditions that, among other functions, provided positive feedback to forebrain neurons and negative feedback to cerebellar neurons. Our data thus support a dynamic astrocytic secretome that maintains a diverse extracellular environment much more complex than previously assumed.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:42

Titel:Foxg1-mediated deficiency of tgf-beta signalling impairs endothelial function through an altered neural secretome

Autoren: Vogel T.(1),Hellbach N.(1),Wahane S.(1),Vezzali R.(1),

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Abstract:
To understand the role of Tgf-beta in forebrain development, we use a FoxG1-cre knock-in mouse line to knock-out Tgfbr2.
FoxG1cre/+; Tgfbr2flox/flox mutants display intracerebral hemorrhages through impaired vasculature, namely atypical clusters of vessels, reduction in branching and number of vessels. These defects are specific to combined reduction of FoxG1 and Tgfbr2. Progenitor proliferation and differentiation appear normal in mutant forebrains. Endothelial cells are ensheathed by pericytes, and cell junctions support vessels. Integrity of the extracellular matrix seems disturbed in mutant animals, as is expression of several genes implicated in angiogenesis, namely Vegf, Fgf2, Igf1, Igf2, Adamts1, Thsb2, Id1, and members of the integrin family.
Endothelial cells and pericytes do not express FoxG1 in significant amounts supporting the hypothesis that vascular defects arise from defective signalling between neurons and vessels, possibly involving an altered secretome. To analyse altered secretion in mutants, we analyse conditioned medium from primary neuronal cultures derived from FoxG1cre/+;Tgfbr2flox/flox and control forebrains. HUVEC stimulated with this conditioned medium in vitro display a branching defect and reduced tube length, confirming our in vivo observations. HUVEC also show impaired migration towards conditioned medium of mutants as compared to that of controls. These phenotypes are partially reverted by supplementation of conditioned media with soluble factors that are misexpressed in Tgfbr2-deficient animals.
Towards the identification of a cause for leaky and unstable vessels in FoxG1cre/+;Tgfbr2flox/flox, we discovered a combination of defects in signalling from neurons and progenitors, proper arrangement of extracellular matrix components as well as cell-matrix adhesion protein expression and arrangement.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:43

Titel:Characterisation of novel hcn1 channel binding proteins

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Abstract:
Rationale: Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are important regulators of the excitability of neurons. The function of these channels depends critically on their subcellular localization, requiring fine-tuned regulation of subcellular channel trafficking by the cellular sorting machinery. Here we searched for binding proteins involved in the regulation of subcellular HCN channel trafficking, thereby focussing on the cortically dominant HCN1 isoform.
Methods: 1) A yeast-two-hybrid (Y2H) analysis using a human embryonic brain cDNA library was applied to identify proteins binding to the HCN1 N-terminus. 2) The HCN1 sequence was systematically screened for potential domains known to be involved in subcellular trafficking decisions. Identified proteins were further probed for HCN1 interaction using Co-IPs and in functional studies using the Xenopus oocyte expression system.
Results: We identified two proteins with known cellular sorting functions that showed strong interaction with HCN1 in vitro: the ubiquitin-ligase Nedd4.2 and the sorting nexin SNX3. Nedd4.2 also co-immunoprecipitated with HCN1 from neocortex, hippocampus and cerebellum, i. e. regions with strong HCN1 expression. Furthermore, if co-expressed with HCN1 in oocytes, Nedd4.2 caused a reduction of the associated current (Ih), suggesting an inhibitory effect on HCN1 surface expression. In contrast, SNX3, although showing overlapping expression with HCN1 in hippocampus and neocortex, did not co-immunoprecipitate with the channels. Also, no effect on Ih was observed, when HCN1 and SNX3 were co-expressed in oocytes.
Conclusions: Nedd4.2 is likely involved in the regulation of HCN1 surface expression, whereas the role of SNX3 still remains to be determined.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:44

Titel:Structural determination of peripheral somatosensory axon terminals via ankyrin-b, not ankyrin-g

Autoren: Engelhardt M.(1),Vorwald S.(1),Hofstettler J.(2),Sobotzik J.(1),Bennett V.(2),Schultz C.(1),

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Abstract:
Axons are subdivided into functionally organized microdomains as required for generation and propagation of action potentials (APs). In the central nervous system (CNS), APs are generated in the axon initial segment (AIS) and propagated by nodes of Ranvier (noR). The membrane adapter proteins ankyrin-B and ankyrin-G play a crucial role as master organizers of AIS and noR. By comparison, little is known on the function of these proteins in axon terminals of the peripheral nervous systems (PNS) and enteric nervous system (ENS). We therefore hypothesized that PNS and ENS axon terminals are organized by distinct members of the ankyrin protein family.

A comprehensive confocal analysis of ankyrin-B and ankyrin-G distribution in combination with various voltage-gated ion channels and other related channel and transmitter proteins was carried out. We discovered a specific distribution of ankyrin-B in somatosensory axon terminals, and noted a striking absence of ankyrin-G in the same structures. Specifically, ankyrin-B was localized along the membrane of axons innervating Meissner corpuscles, Pacinian corpuscles and hair follicle receptors. Furthermore, ankyrin-B expression extended into nociceptive intraepidermal nerve fibers and was found in various ENS cell types. Interestingly, all studied somatosensory terminals were largely devoid of ankyrin-G, indicating that this scaffolding protein does not contribute to organization of mechano-electric transduction zones in the PNS. Voltage-gated ion channels were present in these axon terminals, suggesting that they might be anchored by ankyrin-B instead of ankyrin-G. We propose that ankyrin-B, but not ankyrin-G serves as a major membrane organizer in somatosensory terminals of the PNS.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:45

Titel:Sonic hedgehog signaling for neural tube patterning: where does it come from?

Autoren: Tsikolia N.(1),Otto A.(1),Viebahn C.(1),

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Abstract:
Opposing gradients of sonic hedgehog (shh) and BMP4 are involved in the dorso-ventral patterning of the neural tube. Shh is thought to be secreted by the notochord to induce its own subsequent floor plate expression which, in turn, causes the ventral-to-dorsal gradient of shh activity. However, the source of shh has not been unambiguously defined to date. We studied the early phase of this process by analysing morphology, gene expression and inhibition of the shh pathway in the chick embryo. At stage 4 shh has two expression domains: the midline epiblast of the node area and the presumptive prechordal mesoderm. Beginning at stage 5, the prechordal mesoderm expression extends into the anterior part of the notochord, the epiblast expression domain elongates anteriorly, but the emerging notochord remains shh negative. This suggests that the epiblast domain transforms during node regression directly into the neuroectoderm (floor plate) domain and does not give rise to notochordal expression. At stage 8 shh is expressed in both the floor plate and the notochord except for its posterior part. Chemical inhibition of shh does not change this expression pattern making self-induction an unlikely proposition. Shh expression in the floor plate and in the notochord may thus be caused by mere node regression and shh expression in the floor plate may arise independently from shh secreted by the notochord.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:46

Titel:Bdnf and ngf originating from sensory ganglia promote the outgrowth of cranial motor axons

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Abstract:
Having exited the hindbrain, cranial motor axons grow in association with sensory ganglia to their targets. Previous studies have shown that cranial motor axons grow towards cranial sensory ganglia. Here, we investigated how sensory ganglia influence the outgrowth of cranial motor axons in the chick embryo. We co-cultured rhombomere 8 with a sensory ganglion. Our results show that outgrowth of cranial motor axons from rhombomere 8 was promoted by a number of sensory ganglia, including petrosal, nodose, trigeminal and dorsal root ganglion. Ganglia isolated from late stages had stronger effect on the outgrowth of cranial motor axons than those isolated from early stages. These results demonstrate that the effect of sensory ganglia on cranial motor axons outgrowth is stage-dependent but not ganglion-specific. We next co-cultured rhombomere 8 with beads loaded with neurotrophic factors and observed that outgrowth of cranial motor axons was enhanced through the brain-derived neurotrophic factor (BDNF) or nerve growth factor (NGF). Application of antibodies against these two factors blocked the effect of sensory ganglia on cranial motor axons outgrowth. Our results suggest that BDNF and NGF mediate the outgrowth effect of sensory ganglia on cranial motor axons.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:47

Titel:Secondary radial glial cells and their role in granule cell positioning in the early postnatal dentate gyrus of reeler mutants and wildtype mice

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Abstract:
During dentate gyrus development two different radial glial systems can be distinguished: an embryonic primary radial glial scaffold with long processes spanning from the neuroepithelium near the ventricle up to the pial surface of the dentate gyrus and a secondary radial glial scaffold with rather short processes spanning the granule cell layer during early postnatal development.

While most radial glial cells throughout the brain are important as guides for neuronal migration, the function of secondary radial glial cells for neuronal positioning is not known, yet. One protein influencing granule cell positioning and secondary radial glial cells is the extracellular signaling protein Reelin. By investigating morphological defects in mouse mutants lacking proteins of the Reelin signaling cascade throughout different stages of dentate gyrus development we were able to show that there is an intimate interaction between granule cells and secondary radial glial cells. In addition using conditional knockout mice, we were able to selectively ablate Reelin signaling in neurons or glial cells to investigate how far defects in one cell population affect the other one. These experiments further support the idea of a bidirectional interaction with secondary radial glial cells being important for proper granule cell positioning and, on the other hand, granule cell positioning being important for a proper radial glial scaffold.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:48

Titel:Occurrence of nerve fibers facilitates discrimination of cardiac conductive myocytes on the level of electron microscope

Autoren: Pauza D.(1),Jokubauskas M.(1),Rysevaite K.(1),Saburkina I.(1),Inokaitis H.(1),Pauziene N.(1),

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Abstract:
Fluorescent immunohistochemistry on the cardiac conduction system (CCS) in whole mount preparations of mouse heart demonstrates a particularly dense and complex network of nerve fibers (NFs) and conductive cardiac myocytes (CCMs) in sinuatrial nodal region (SAN) and adjacent areas around the root of right cranial vein. The present study was designed to investigate the morphologic and cytochemical patterns of NFs and CCMs using fluorescent techniques coupled with electron microscope (E.M.) evaluation. Adrenergic and cholinergic NFs together with CCMs were identified using primary antibodies for protein gene product 9.5 (PGP 9.5), tyrosine hydroxylase (TH), choline acetyltransferase (ChAT), and hyperpolarization activated cyclic nucleotide-gated potassium channel 4 (HCN4), respectively. Amid CCMs immunoreactive for HCN4, E.M. data demonstrated dense distribution of NFs immunoreactive for ChAT and TH. In addition, E.M. revealed that the mouse SAN contained exclusively unmyelinated NFs, in which the majority of axons possess varicosities with clear mediatory vesicles that can be classified as cholinergic ones. En passant synapses were the only interrelationship of CCMs with NFs in mouse SAN area. In general, the morphologic pattern of innervation of mouse CCMs identified using electron microscopy corresponds well to the dense network of NFs demonstrated by fluorescent immunohistochemistry in mouse SA nodal and adjacent areas. The complex and extraordinarily dense innervation of CCMs in mouse SAN underpins the importance of neural regulation for the CCS. In conclusion, the occurrence of NFs nearby cardiac myocytes with sparse myofibrils and electron-lucid cytoplasm may serve as reliable extracellular criterion for discrimination of CCMs on E.M. level.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:49

Titel:The complement system contributes to the pathology of experimental autoimmune encephalomyelitis by triggering demyelination and modifying the antigen-specific t and b cell response

Autoren: Kuerten S.(1),Hundgeburth L.(1),Wunsch M.(1),Rovituso D.(1),Recks M.(1),Addicks K.(1),

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Abstract:
So far, studies of the human autoimmune disease multiple sclerosis (MS) have largely been hampered by the absence of a pathogenic B cell component in its animal model, experimental autoimmune encephalomyelitis (EAE). To overcome this shortcoming, we have previously introduced the myelin basic protein (MBP)-proteolipid protein (PLP) MP4-induced EAE, which is B cell and autoantibody-dependent. Here we show that MP4-immunized wild-type C57BL/6 mice displayed a significantly lower disease incidence when their complement system was transiently depleted by a single injection of cobra venom factor (CVF) prior to immunization. Considering the underlying pathomechanism, our data suggest that the complement system is crucial for MP4-specific antibodies to trigger CNS pathology. Demyelinated lesions in the CNS were colocalized with complement depositions. In addition, B cell deficient JHT mice reconstituted with MP4-reactive serum showed significantly attenuated clinical and histological EAE after depletion of complement by CVF. The complement system was also critically involved in the generation of the MP4-specific T and B cell response: in MP4-immunized wild-type mice treated with CVF the MP4-specific cytokine and antibody response was significantly attenuated compared to untreated wild-type mice. Taken together, we propose two independent mechanisms by which the complement system can contribute to the pathology of autoimmune encephalomyelitis. Our data corroborate the role of complement in triggering antibody-dependent demyelination and antigen-specific T cell immunity and also provide first evidence that the complement system can modify the antigen-specific B cell response in EAE and possibly MS.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:50

Titel:Role of formyl peptide receptors in innate immune response after bacterial meningitis

Autoren: Brandenburg L.(1),Pscheidl S.(1),Oldekamp S.(1),Jansen S.(1),Tauber S.(2),Pufe T.(1),

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Abstract:
Bacterial meningitis is despite progress in research and the development of new treatment strategies still a cause of severe neuronal sequelae right up to death. The brain is protected from penetrating pathogens by the blood-brain barrier (BBB) and by the innate immune system. The representatives of the innate immune system in the brain are glial cells, astrocytes and microglia cells. The invading pathogens are being recognized via pattern recognition receptors such as formyl peptide receptors that are expressed by glial immune cells of the central nervous system (CNS). The expression of the G-protein coupled chemotactic formyl peptide receptors is up-regulated after bacterial meningitis, but the consequence of receptor for progression of inflammation are far from clear.
Therefore, we used formyl peptide receptors (mFPR1 and 2) deficient mice to investigate the role receptors in lethality and inflammation after pneumococcal meningitis. We compared the lethality rate and bacterial growth between both mice strains and analysed the inflammation in the cortex and hippocampus using immunohistochemistry and realtime RT-PCR.
Our results showed no change of lethality after bacterial meningitis for mFPR1/2-deficient mice compared to wildtype mice. But the mFPR1/2-deficient mice showed significant increased glial cell activation, whereas the immune response including cytokine and antimicrobial peptides expression are decreased after bacterial meningitis.
Altogether, the results suggest that the formyl peptide receptors play an important part in the innate immune response against pathogens in CNS bacterial infections.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:51

Titel:What a single neuron tells us about synaptic network activity- automated analysis of whole cell current clamp recording

Autoren: Drakew A.(1),Maier U.(1),Tippmann A.(1),Frotscher M.(1),

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Abstract:
Postsynaptic potentials (PSPs) as well as action potentials (APs) recorded from a patch-clamped neuron represent the spontaneous synaptic network activity at the single cell level. This spontaneous synaptic activity reflects the actual state of plasticity of the contributing synapses and cells. Therefore, factors interfering with mechanisms of synaptic plasticity should alter the spontaneous activity recorded from a neuron. We aimed to develop a fully automated method allowing for effective quantitative analysis of such recordings. However, a quantitative analysis of the resulting voltage traces is demanding due to the large amount of events and the significant overlap of these events, which reside on a fluctuating baseline.
The suggested approach performs the analysis in 3 steps: 1. Detection of events, based on a voltage-deconvolution approach (Richardson and Silberberg (2008) J. Neurophysiol. 99: 1020–1031) 2. Definition of the baseline 3. Quantitative measurements on all detected events. The distributions of these parameters represent the synaptic activity in one neuron in a quantitative manner that can be compared between cells and conditions.
Using this method we want to analyze patch-clamp recordings of mossy cells in entorhino-hippocampal slice cultures of synaptopodin knockout mice, which do not form a subcellular organelle, the spine apparatus. This organelle is a regular component of the complex spines postsynaptic to mossy fiber boutons. The spine apparatus has been suggested to contribute to potentiation at excitatory synapses. This implies changes in the distribution of PSP amplitudes in recordings from synaptopodin mutant mice, if the spine apparatus is of relevance for spontaneous neuronal communication.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:52

Titel:Accessing back nerves eased by knowing their homologous structures

Autoren: Steinke H.(1),Saito T.(2),Miyaki T.(2),Nawa S.(2),Umemoto K.(2),Miyakawa K.(2),Wakao N.(2),Asamoto K.(2),Nakano T.(2),

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Abstract:
For a treatment in the thoraco-lumbo-sacral region back nerves are accessed. Whereas bones and muscles can be easily visualised by the use of radiology, nerves can't. The structures of the back change shape from segment to segment. They rose from an undifferentiated layout forming segmental homologues in adults. For the R. posterior n. spinalis (RPNS), beside a simple dichotomy described in the textbooks, a triplication has also been described in the past. To support this thesis, correlating structures of such threefold branching are shown here.
Medial branches of the RPNS reach to the spinous process (proc.) and to the facet joints with a medial muscle compartment (MC; e.g. M. spinalis, Bulbus erector spinae). They pass lumbarly between the mammillary proc. and the accessory proc. They find thoracic homologues, the superior articular proc. and the transversal proc., which are connected by ligaments covering the medial branches.
At the thoracic level, lateral branches pursuing the ribs, and lumbar, their homologues, the costal processes. Lateral branches innervate a lateral MC (M. iliopsoas).
Intermedial branches reach an intermedial MC (the Longissimus, basically), divide ventrally to this MC, and form long branches to the skin far from the nerve\'s origin, penetrating and thus dividing the lateral and the intermedial MC.
While medial branches are largely thoraco-sacral, their lumbar homologues are small, due to the homologous MC. Thus, the intermedial and the lateral branches are easy to find there, while the medial branch is not. This explains why the lumbar intermedial branch is to be regarded as a medial branch. Homologues clarify this theoretical misinterpretation. Their recognition, however, practically eases approaching the RPNS.

Kategorie: Lecture

Rubrik: Neurobiology/Development
Abstract Nr.:53

Titel:Occipital somites guide motor axons of the accessory nerve in the avian embryo

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Abstract:
The nervus accessorius displays a unique organization in that its axons ascend along the rostrocaudal axis after exiting the cervical spinal cord and medulla oblongata and thereafter project ventrally into the periphery at the first somite level. Little is known about how this organization is achieved. We here investigated the role of somites in guidance of motor axons of the nervus accessorius using heterotopic transplantations of somites in avian embryos. After an occipital somite (somite 2-4) was grafted to the position of the first somite, the formation of the nervus vagus and accessorius was affected. Our observation reveals that occipital somites guide the pathfinding of motor axons of the nervus accessorius by preventing their ventral projection at the level of occipital somites.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:54

Titel:Degeneration of brainstem nuclei in huntington's disease

Autoren: Rüb U.(1),Seidel K.(1),Bouzrou M.(1),Stratmann K.(1),Korf H.(1),

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Abstract:
Clinical findings of previous studies have suggested a degeneration of select brainstem nuclei in Huntington's diseases (HD). However, comprehensive pathoanatomical data on the brainstem of HD patients are still missing. We therefore investigated the brainstem of eight clinically diagnosed and genetically confirmed HD patients and of fourteen control individuals without histories of neurological or psychiatric diseases. From all cases serial sections of the brainstem were prepared and stained for lipofuscin pigment (aldehyde-fuchsin) and Nissl material (Darrow red) to assess nerve cell loss in the HD patients. Neuronal and axonal aggregates were visualized by immunostaining for the proteasomal shuttle protein p62 in combination with the tau-AT270 antibody as axonal marker. Our investigations revealed consistent neuronal loss in the pontine nuclei, reticulotegmental nucleus of the pons, inferior olive, in the area for excitatory burst neurons for horizontal saccades, raphe interpositus nucleus, superior olive, and vestibular nuclei of all HD patients. p62 immunoreactive neuronal intranuclear inclusions were present in all (affected and spared) brainstem nuclei of the HD patients, but not in the controls. p62 immunoreactive axonal inclusions were most prevalent in brainstem fiber tracts associated with degenerated brainstem nuclei of HD patients. Our novel findings clearly show that the brainstem is among the targets of the neurodegenerative process in HD. Its degeneration can account for a number of hitherto unexplained clinical symptoms (i.e. cerebellar, oculomotor and vestibular symptoms), while the formation of axonal aggregates most likely may be crucial event in the pathogenesis of neurodegeneration associated with HD.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:55

Titel:Borna disease virus-induced neuronal degeneration is dependent on the host genetic background and prevented by soluble factor(s)

Autoren: Heimrich B.(1),Wu J.(2),Schwemmle M.(2),

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Abstract:
Infection of newborn rats with BDV results in selective degeneration of granule cell neurons of the dentate gyrus (DG). To study cellular counter mechanisms that might prevent this pathology, we screened for rat strains resistant to this BDV-induced neuronal degeneration.
We infected hippocampal slice cultures of different rat strains with BDV and analyzed for the preservation of the DG. Whereas infected cultures of five rat strains, including Lewis (LEW) rats, exhibited a disrupted DG cytoarchitecture, slices of three other rat strains, including Sprague-Dawley (SD) rats, were unaffected, although efficiency of viral replication was comparable. These rat strain-dependent differences in vulnerability were replicated in vivo in neonatally-infected LEW and SD rats.
In a second set of experiments, we could show that conditioned media from uninfected cultures of both LEW and SD rats can prevent from BDV-induced DG damage in infected LEW hippocampal cultures, whereas infection with BDV suppressed the availability of these factors from LEW but not in SD hippocampal cultures.
To gain further insights into the genetic basis for this rat-strain dependent susceptibility, we analyzed DG granule cell survival in BDV-infected cultures of hippocampal neurons derived from the F1 and F2 offspring of the crossing of SD and LEW rats. Genome-wide association analysis revealed one resistance locus on chromosome (chr) 6q16 in SD rats and, surprisingly, a locus on chr3q21-23 that was associated with susceptibility.
Thus, BDV-induced neuronal degeneration is dependent on the host genetic background and is prevented by soluble protective factors in the disease-resistant SD rat strain.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:56

Titel:Transplantation of human umbilical cord blood cells after perinatal hypoxic-ischemic brain injury – positive effects on neuronal survival, inflammation and glial activation

Autoren: Rosenkranz K.(1),May C.(2),Kumbruch S.(3),Marcus K.(1),Meier C.(4),

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Abstract:
Perinatal hypoxic–ischemic brain injury (HI) is an important cause of neurological deficits in the early period of life. As efficient clinical or pharmaceutical strategies to prevent or reduce the outcome of HI are limited, the development of new therapies is of utmost importance. To evolve innovative therapeutic concepts, elucidation of the (patho-)mechanisms contributing to the neurological impairments upon hypoxic–ischemic brain injury is necessary. Using a 2D-DIGE based proteomic approach, proteins affected by perinatal HI were analyzed in an experimental rat model. Among the regulated proteins, Calcineurin A, Coronin-1A, and GFAP were identified and these are known to be involved in the most detrimental processes following HI, i.e. apoptosis and glial activation. Changes in these pathways were then analyzed in response to transplantation of human umbilical cord blood (hUCB) cells demonstrating beneficial effects of these cells on neuronal survival, inflammation and astroglial activation.
Taken together, the results of this study contribute to clarification of the complex mechanisms following perinatal HI and, thereby, to identify new molecular targets of intervention. The relevance of these findings for disease and treatment was demonstrated by changes in exactly these pathways upon transplantation of hUCB cells, representing potential novel cell therapies in the treatment of perinatal HI.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:57

Titel:Carbonic anhydrase 2 and 4 are key enzymes in murine sperm motility and fertility

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Abstract:
Carbonic anhydrase catalyzes the reversible hydration of CO2 into HCO3-, thus regulating the HCO3- concentration in fluid composition and in several cells of the organism. HCO3- is also a fundamental factor in sperm maturation and is present in the seminal fluid and in the oviduct. Downstream effects of HCO3-, inducing sperm motility, with increased beat frequency during the first 30 seconds in the presence of HCO3- and CO2, are already well-described. It is known that extracellular CAIV and intracellularly-located CAII are involved in HCO3- induced signaling in sperm. We generated for the first time a double-deficient CAII/CAIV knockout line to analyze mice fertility and sperm motility. Double knockout offspring are viable, although weight development, testis weight and fertility are reduced in comparison to wild type. While velocity, percentage of motility and fast progressive sperm were significantly reduced in double knockout sperm, the deficient sperm population showed an increase in the percentage of immotile sperm by a constant cell concentration. The HCO3- induced pathway could not only be mimicked in double knockout sperm, but the effects were even increased by treating CAII-deficient sperm with phospholipase C to cut lipid-anchored CAIV from the sperm membrane. These findings suggest the possible compensatory induction of another CA isoform for the lack of CAII and CAIV in double-deficient mice. The results show that CAII and CAIV are key enzymes in murine sperm motility and fertility.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.: 58

Titel:Maternal diabetes mellitus influences fatty acid metabolism in rabbit preimplantation embryos

Autoren: Schindler M.(1),Penzialek M.(1),Plösch T.(2),Navarrete Santos A.(3),Fischer B.(1),Navarrete Santos A.(1),

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Abstract:
In the western world abnormal maternal glucose regulation occurs in 3-10% of pregnancies. It is highly likely that intrauterine exposure to hyperglycaemia contributes to the increased prevalence of obesity in offspring (“Developmental origins of health and disease" (DOHaD) hypothesis). The links between glucose and lipid metabolism during embryonic and fetal development, however, need to be better characterized.
We have studied the effects of hyperglycaemia in vivo on early embryo development by inducing type I diabetes through alloxan treatment of female rabbits. In these rabbits the serum triglyceride concentration was increased. More astonishing was a massive intracellular lipid accumulation in embryoblast (ICM) and trophoblast cells of six day old blastocysts. The expression of genes involved in lipid metabolism, like FATP4, FABP4 and perilipin/adipophilin, was elevated in diabetic blastocysts. However, expression of FASN, a key enzyme for de-novo synthesis of fatty acids, was reduced. To analyse the influence of hyperglycaemia on these genes and on lipid accumulation, we stimulated blastocysts with 0, 10, 25mM glucose in vitro. Expression of adipophilin and FASN were increased in blastocysts cultured with 25mM glucose. Furthermore, the amount of lipid vesicles was increased compared to blastocysts cultured without glucose. On the contrary, when blastocysts from diabetic mothers were cultured without glucose, lipid vesicles were reduced compared to in vivo diabetic blastocysts.
Our study shows the decisive effect of glucose as determining factor for fatty acid metabolism in preimplantation embryos. Long-lasting consequences, like obesity in later life, need further investigation.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:59

Titel:A possible mouse model for researching the genesis of the double lumen aortic arch malformation

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

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Abstract:
Double lumen aortic arch (DLAA) is a rare congenital malformation, which is often associated with other cardiovascular anomalies. Until recently, it was accepted that mice do not feature DLAAs. Therefore there is no mouse model for studying its genesis. Since we recently diagnosed a spontaneous developed DLAA in a wild-type mouse fetus, we decided that it is worth to look for a knock out strain that fits for studying DLAA malformations. In this study, we present first results of screening four knock out strains, which show severe cardiovascular malformations - and thus produce fetally or neonatally lethal homozygous offsprings – for their ability to serve as models to research DLAA malformations. We screened the great intrathoracic arteries of 14.5 dpc Arid2 -/-, Csrp2bp -/-, NF1 -/-, and Mks1 -/- mouse fetuses. Employing the high-resolution episcopic microscopy (HREM) technique we created of 3 embryos of each strain digital volume data with a voxel size of 3 x 3 x 3 µm3 and virtual 3D models of their great intrathoracic arteries. 15 of the 16 embryos showed malformations of the pharyngeal arch arteries. One of the Mks1 -/- embryos featured symmetric, left and right-sided aortic arches. Each aortic arch gave rise to the ipsilateral common carotid and subclavian arteries. The segment of the right aortic arch located between the origin of the right common carotid and right subclavian artery showed two lumina. Thus, our screen suggests that Mks1 -/- mice might represent a decent model for researching DLAA malformations.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:60

Titel:Bhlh protein atoh8 is involved in the adult myogenesis transcriptional network

Autoren: Balakrishnan-Renuka A.(1),Böing M.(1),Yusuf F.(1),Patel K.(2),Otto A.(2),Morosan-Puopolo G.(1),Zoidl G.(3),Brand-Saberi B.(1),

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Abstract:
ATOH8 is a member of the Atonal family of basic Helix-Loop-Helix transcription factors. Although the protein is well characterized in relation to neurogenesis, its involvement in other developmental contexts is not well understood. Previous work in our laboratory has shown that ATOH8 is expressed in the somite of chicken embryos and downregulation of ATOH8 in the lateral somite at the trunk level results in a blockage of differentiation and causes cells to be maintained in a predetermined precursor state. In the present study, we show the expression profile of ATOH8 during adult myogenesis. The satellite cells in vitro dynamically express ATOH8 while the cells undergo the process of differentiation, as evidenced by the co-expression of the protein together with Pax7 and Myogenin. We also report the re-appearance of the ATOH8 expression in skeletal muscle undergoing regeneration in vivo, which all together point towards an important role for ATOH8 in the regeneration process. Furthermore, ATOH8 is also expressed in cultured C2C12 mouse myoblasts and dramatically decreases in differentiating myoblasts. Hence we propose a role for ATOH8 during the transition of myoblasts from the proliferation to the differentiation phase. We also demonstrate that ATOH8 expression in the somite is regulated by Notch signaling. In conclusion, we speculate that ATOH8 is a bHLH protein, which could be required to fine regulate the balance between skeletal myogenesis and self-renewal of satellite cells and of the myogenic progenitors during embryonic myogenesis.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.: 61

Titel:The enigma of the neurenteric canal: the common marmoset monkey (*Callithrix jacchus*) provides a pivotal missing link

Autoren: Viebahn C.(1),Tsikolia N.(1),Drummer C.(2),Behr R.(2),

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Abstract:
The neurenteric canal, discovered by Lieberkühn in the 19th century, is still known primarily as a morphological entity with a specific topographical context. Positioned immediately posterior to the emerging notochordal process it is thought to constitute – in a variety of species – a transient communication channel between two lumina of entirely different nature: the cavity of the developing gut on the ventral side of the embryo, and the canal of the developing central nervous system on the dorsal side. As central as it is in terms of position, the neurenteric canal has, to date, no known function; in comparative embryology or pathology, though, it provides coordinates for defining analogous structures during early vertebrate neurulation, or offers explanations for congenital defects. For the human embryo, the occurrence of a neurenteric canal has long been controversial, due not least to the difficulty in obtaining adequately preserved specimens at the stages in question (Carnegie stages 8 and 9, found at 23–25 days post fertilisation). This study presents the first clear-cut evidence of a patent neurenteric canal and the cellular composition of its lining in an optimally fixed, rare specimen of a higher primate at a morphologically defined stage equivalent to the late Carnegie stage 8. The available evidence in the human can now be sorted in the light of the present findings and used "pivotally" in the literal sense to define homologous structures amongst transient axial organs of gastrulation and neurulation in amniotes including reptiles.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:62

Titel:Myocilin modulates programmed cell death during retinal development and after retinal damage

Autoren: Koch M.(1),Rosenhammer B.(1),Koschade S.(1),Braunger B.(1),Volz C.(2),Jägle H.(2),Tamm E.(1),

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Abstract:
Purpose: To investigate the role of myocilin in the mouse retina. Myocilin is a secreted glycoprotein of the olfactomedin family whose biological function(s) are still largely unclear.

Methods: Myocilin-deficient mice (Myoc-/-) and Myoc-/-; βB1-Crystallin-Myocilin mice with ocular overexpression of myocilin were characterized and analyzed by real-time RT-PCR, semithin sectioning and electroretinography (ERG). Apoptosis of retinal neurons was visualized by TUNEL-labeling and quantified. Western blotting was used to investigate different signaling pathways. In vitro experiments were performed with RGC-5 cells. Apoptosis of RGC was induced by NMDA-injection and excitotoxicity, while apoptosis of photoreceptors was induced by light damage.

Results: During postnatal synaptogenesis, apoptotic death of retinal neurons throughout the retina was significantly decreased in Myoc-/- pups. The decrease resulted in a significantly higher number of retinal ganglion cell (RGC) perikarya and their axons in the optic nerve, as well as in an increased thickness of outer and inner nuclear layer in adult Myoc-/- mice compared to wild-types. In contrast, myocilin-deficient mice with simultaneous ectopic overexpression of myocilin from the lens (Myoc-/-; βB1-Crystallin-Myocilin) did not show differences in retinal structure or developmental apoptosis compared to wild-type mice. In vitro, recombinant myocilin promoted apoptosis of RGC-5 cells, an effect that could be blocked by myocilin antibodies. The amounts of pJNK were decreased in P10 Myoc-/- mice when compared to wild-type animals, while no differences were observed when canonical Wnt/β-catenin, TGF-β of PI3K-Akt signaling were investigated. Myocilin-deficient mice showed less apoptosis in both damage models.

Conclusions: Myocilin modulates programmed cell death during retinal development and after damage

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:63

Titel:Human prostate cancer in a clinically relevant xenograft mouse model: identification of beta(1,6)-branched oligosaccharides as a marker of tumor progression

Autoren: Lange T.(1),Schumacher U.(1),

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Abstract:
Prostate cancer (PCa) is the most common malignancy in males and largely incurable after metastatic spread has occurred. It is therefore of particular clinical interest to study the mechanisms of metastasis formation in suitable animal models. Thus, we have established s.c. xenograft models using four PCa cell lines in immunodeficient mice. Tumor growth and metastasis formation were quantified and as altered glycosylation patterns have been associated with metastasis formation in several other malignancies, PCa cells were profiled by a quantitative real-time PCR (qRT-PCR) glycosylation array and compared with normal human prostate cells. The activity of up-regulated glycosyltransferases was analyzed by their sugar residues end products using lectin histochemistry on primary tumors and metastases in the animal experiments and on 2,085 clinical samples.
PC-3 cells produced the largest number of spontaneous lung metastases, followed by LNCaP, LuCaP23.1 and DU-145. qRT-PCR revealed an up-regulation of b1,6-Nacetylglucosaminyltransferase-5b (Mgat5b) in all PCa cell lines. Mgat5b products (beta-(1,6)-branched oligosaccharides), however, were predominantly detectable in metastatic xenografts as shown by increased binding of Phaseolus vulgaris leukoagglutinin (PHA-L). 86.5 % of PCa patients were PHA-L positive. PHA-L intensity correlated with serum prostate-specific antigen and a cytoplasmic staining negatively affected disease-free survival.
In conclusion, we show a novel xenograft model for human PCa respecting the complete metastatic cascade. Specific glycosylation patterns reveal Mgat5b products as relevant markers of both metastatic competence in mice and disease-free survival in patients. We firstly describe Mgat5b in PCa indicating a significant biologic importance of beta-(1,6)-branched oligosaccharides in this disease.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:64

Titel:Trastuzumab has anti-metastatic and anti-angiogenic activity in a spontaneous metastasis xenograft model of esophageal adenocarcinoma

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Abstract:
One of the main challenges of cancer therapy is the prevention of severe side effects often observed during conventional chemotherapies that affect non-malignant cells also. Therefore, a range of targeted therapies have been developed utilizing unique tumor cell characteristics for the mode of pharmacological action. One example of targeted therapy is the treatment of Her-2/neu-positive breast cancer patients with the humanized monoclonal antibody trastuzumab (Herceptin ®) that directly targets the extracellular domain of Her-2/neu and shows sometimes a remarkable therapeutic efficacy. Interestingly, an over-expression of Her-2/neu has meanwhile also been described in 10–40 % of patients with esophageal adenocarcinoma. We have therefore investigated the effects of trastuzumab on proliferation, neoangiogenesis and metastatic spread of an esophageal adenocarcinoma cell line (PT1590) in vitro and in vivo. PT1590 revealed an amplified copy number of the HER-2 gene c-erbB2. HER-2/neu over-expression occurred in xenograft tumors and spontaneous lung metastases. PT1590 proliferation was significantly inhibited by trastuzumab in vitro. In vivo, tumor weight, tumor volume, microvessel density and the number of spontaneous lung metastases significantly decreased after three weeks of treatment. Our findings demonstrate anti-proliferative, anti-metastatic and anti-angiogenic effects of trastuzumab in a xenograft tumor model of esophageal adenocarcinoma encouraging its clinical use for targeted therapy in cancers other than breast.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:65

Titel:Vascular and lymphatic markers: time series in human skin and choroid

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

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Abstract:
Introduction: Immunohistochemistry in human donor tissue can cause false negative results due to post-mortal tissue alterations. This is critical if one has to decide about presence or absence of lymphatics in the posterior uvea since available results are contradictory. Here, we tested a time series in human skin samples and subsequently applied our results in human choroid.

Methods: Meeting the Declaration of Helsinki, human skin was collected during surgery and kept in phosphate buffered saline at room temperature. Specimens were fixed 5, 7, 12, 24 hrs post surgery and prepared for single and double immunohistochemistry of the following markers: CD31, PLVAP, LYVE-1, PROX-1, VEGFR3. Human choroids (10-14 hrs post mortem; age 55-59; n=2) were screened for PROX-1 and VEGFR3. Confocal laser-scanning microscopy was used for documentation.

Results: In human skin, the vascular endothelial markers CD31 and PLVAP showed stable immunoreactivity 24 hrs after surgery, as did the lymphatic markers LYVE-1, PROX-1, and VEGFR3. Double immunohistochemistry revealed the presence of PROX-1 and VEGFR3 in lymphatic endothelium exclusively, while CD31 was detected in both lymphatic and vascular endothelium. PLVAP was present in vascular endothelium only. In human choroid, PROX-1 and VEGFR3 double immunohistochemistry revealed absence of both markers.

Conclusion: Investigated markers showed reliable results 24 hrs after tissue harvest, suggesting that post-mortal alterations are not critical in the time frame investigated. Therefore, the absence of lymphatics in human choroid is most likely not caused by post-mortal alterations in the donor tissue, but indeed indicates absence of lymphatics in the posterior uvea (studysupport: PMU-FFF, Adele-Rabensteiner-Foundation)

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:66

Titel:Increased heart weight in newborn guanylyl cyclase/natriuretic peptide receptor a knockout mice is due to increased number, not size of cardiomyocytes

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Abstract:
Atrial natriuretic peptide (ANP) elicits its responses by binding to guanylyl cyclase/natriuretic peptide receptor A (GC-A). The phenotype of adult GC-A knockout mice is characterized by hypertension and left and right ventricular hypertrophy. Interestingly, also newborn GC-A deficient mice have increased heart weights which raises the question whether this is due to an increased number or an increased size of cardiomyocytes.
To address this, hearts of newborn wildtype or global GC-A knockout mice were examined by design-based stereology using light and electron microscopy. In GC-A deficient mice, the ratios of ventricular weight to body weight as well as the total volumes of myofibrils, mitochondria, sarcoplasma and nuclei related to body weight were significantly enhanced. The total number of cardiomyocytes related to body weight was significantly higher in GC-A deleted mice compared to wildtype (WT: 651586 +/- 131624; KO: 1060845 +/- 185858; p = 0.0003), whereas the number-weighted mean volume of cardiomyocytes (WT: 6316 µm3 +/- 1338; KO: 5902 µm3 +/- 785) and cardiac nuclei (WT: 600 µm3 +/- 113; KO: 668 +/- 147) were similar. Our data clearly demonstrate that hyperplasia and not hypertrophy causes the increase in heart weight in GC-A knockout mice. We postulate that ANP modulates cardiomyocyte proliferation via GC-A during perinatal development.

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:67

Titel:Chemosensation in urethral cholinergic brush cells

Autoren: Deckmann K.(1),Krasteva-Christ G.(1),Rafiq A.(1),Filipski K.(1),Bschleifer T.(2),Althaus M.(3),Fronius M.(3),Kummer W.(1),

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Abstract:
We previously have identified a cholinergic epithelial cell in the urethra that exhibits structural markers of respiratory chemosensory cells (“brush cells”) and expresses components of the canonical taste transduction signaling cascade. Here, we investigated the expression of specific taste receptors in the urethral epithelium and the response of the putative chemosensory cells to gustatory stimuli.
RT-PCR of abraded urethral epithelium revealed mRNAs coding for several taste receptors. Accordingly, responses to various stimuli were investigated by CLSM recording of free intracellular calcium concentration ([Ca2+]i). Candidate chemoreceptor cells from two different strains of ChAT-eGFP mice (ChAT = choline acetyltransferase) were identified by their eGFP fluorescence, and from wild-type mice by antibody labeling (FITC) of an extracellular domain of the cation channel TPRM5. 26/32 (81%) cells responded to ATP (0.5 mM) with an increase in [Ca2+]i, 30/34 (88%) to denatonium benzoate (25 mM; bitter compound), and 23/27 (85%) to glutamate (25 mM; “umami”). The response to denatonium benzoate was blocked by a specific TRPM5 channel blocker (TPPO; 0.25 mM). In addition, we achieved an initial characterization of the electrophysiological profile in whole cell patch clamp recording. These data indicate that the identified cholinergic epithelial cell in the urethra is a chemosensory cell responding to gustatory stimuli such as bitter substances and umami. We interpret this cell type as a sentinel at the entrance to the urogenital tract initiating protective mechanisms by acetylcholine release.
Funding: LOEWE Schwerpunkt “Non-neuronale cholinerge Systeme”

Kategorie: Lecture

Rubrik: Re-/Degeneration – Cell biology
Abstract Nr.:68

Titel:Bitter chemosensation in the murine trachea

Autoren: Rafiq A.(1),Canning B.(2),Hartmann P.(1),Weitz A.(1),Deckmann K.(1),Kummer W.(1),Krasteva-Christ G.(1),

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Abstract:
Tracheal chemosensory brush cells express bitter receptors (Tas2R family) and further components of the taste transduction cascade. These cells are cholinergic and in close contact with intra-epithelial sensory nerve fibers carrying nicotinic receptors (nAChR). We previously showed that application of the Tas2R105 ligand cycloheximide causes epithelium dependent decrease in respiratory rate involving nicotinic transmission (Krasteva et al., PNAS 108(23):9478-83, 2011).
Here we investigated the role of Tas2R108 in bitter sensation in mouse trachea by monitoring respiratory rate and effects on [Ca2+]i. Isolated tracheal brush cells respond to the Tas2R108 ligand, denatonium (10 mM), by an increase in [Ca2+]i. Mucosal application of denatonium causes epithelium dependent decrease in respiratory rate. However, mecamylamine (nAChR antagonist) treatment augmented the occurrence of short depressions in respiration (“respiratory events”) in the presence of denatonium. In addition to brush cells, isolated ciliated epithelial cells respond to denatonium by an increase in [Ca2+]i,¬¬ and decrease in particle transport speed on the mucosal surface of the isolated mouse trachea. In addition, sensory neurons from dorsal root and jugular-nodose ganglia express mRNA for Tas2R108, but not TasR105, along with other components of the bitter sensation cascade. Isolated sensory neurons also respond to denatonium (10 mM) by an increase in [Ca2+]i.
These data demonstrate multiple sites of denatonium chemosensation in the murine trachea. Brush cells mediate reduction in respiratory rate involving cholinergic, nicotinic transmission. Additional epithelial effects lead to inhibition of ciliary driven particle transport, and sensory neurons are also direct targets of denatonium.
Funding: Deutsches Zentrum für Lungenforschung

Kategorie: Lecture