Lecture Abstracts

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Nederlandse Anatomen Vereniging

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Example:

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Abstracts

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Abstract Nr.:6

Titel:CD4+T cell-mediated neuroprotection following peripheral nerve injury

Autoren: Jones K.(1),

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Abstract:
To understand the beneficial role for the peripheral immune system in motoneuron reparative processes.
Use of the mouse facial motoneuron (FMN) injury paradigm, which involves a peripheral nerve injury outside the blood-brain-barrier, in conjunction with immunodeficient mouse models (including the recombinase-activating gene-2 knockout (RAG-2 KO) mouse which lacks functional T and B cells; Serpe et al., 1999) to assess immune involvement in neuroprotection.
The CD4+ effector Th2 cell is the critical cell needed for FMN rescue from axotomy-induced cell death through an antigen-specific process requiring peripheral activation followed by central re-activation and brain-derived neurotrophic factor (BDNF) as the molecule required for Th2 cell-mediated FMN rescue. Lymph node analysis indicates that both a Th1 and Th2 cytokine profile develops in response to peripheral nerve injury. Functional recovery from facial paralysis induced by facial nerve crush injury is significantly impaired in immunodeficient animals, but is restored to wild-type (WT) after reconstitution of the immune system.
These findings provide the foundation for a working model of CD4+ T cell-mediated motoneuron survival and axonal regeneration after injury. Key to this model is the new concept that CD4+ effector T cell subsets play distinctive roles in motoneuron reparative processes, with the Th2 cell mediating FMN survival through a central BDNF-dependent process and the Th1 cell mediating functional recovery through participation in the lesion site pro-inflammatory response.

Kategorie: Lecture

Rubrik: 1.Main Topic I
Abstract Nr.:8

Titel:T helper cells stimulate axon regeneration via interleukin-4 in an AKT/MAPK-dependent manner

Autoren: Hendrix S.(1),

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Abstract:
It has been suggested that T cell injections and vaccination strategies with encephalitogenic antigens contribute to protection from secondary damage after non-autoimmune brain and spinal cord injury, however, these studies have been challenged by recent findings demonstrating that the approach includes severe detrimental effects. These contradictory data suggest that a specific molecular crosstalk between the immune system and the nervous system critically determines the ultimate outcome of T cell actions in the brain. Here we report that IL-4, released by T cells independently of their antigen specificity, stimulates substantial fiber regrowth in the lesioned spinal cord. IL 4 receptor ko animals, mice with selective mutations in the IL-4 signal transduction cascade, inhibitory antibodies, and delivery of IL-4 both in vitro and in vivo were used to identify this cytokine as the molecule responsible for T cell mediated axon outgrowth. This effect was independent of IL-10 and IL-13 and not the result of increased local release of neurotrophins but of T cells conveying regeneration via IL 4 dependent modulation of neurotrophin signaling. In vitro analyses revealed that the T cell and the IL-4 effects were independent of the classical IL-4 receptor-associated stat-6 signalling pathway but mediated by AKT/MAPK signalling. Locomotion analysis revealed significantly improved neurological outcome after lesion in mice treated with IL-4+ T cells. Our results feature IL-4 as a key player in T cell mediated axon reorganization and open the door to the design of novel CNS repair strategies.

Kategorie: Lecture

Rubrik: 1.Main Topic I
Abstract Nr.:9

Titel:Serotonin acutely elevates intracellular calcium concentration and augments CCL2 production in murine alveolar macrophages

Autoren: Mikulski Z.(1),Zaslona Z.(2),Cakarova L.(2),Hartmann P.(1),von Wulffen W.(2),Kummer W.(1),

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Abstract:
Serotonin (5-HT) modulates immune responses and inflammatory cascades. However, the effects of 5-HT on alveolar macrophages (AM) remain elusive.
In our study the expression profiles of 5-HT receptors in C57BL/6N mouse AM and alveolar epithelial cells (AEC) were determined and the responses to stimulation with 5-HT were examined. Expression of 5-HT receptor subunits was investigated by quantitative real time PCR (qRT-PCR) and changes in intracellular calcium concentrations ([Ca2+]i) were monitored by the fura-2 method. Cytokine secretion was assessed by a dot-blot based assay and validated by ELISA.
The qRT-PCR revealed expression of receptor subunits 5HT2A and 5HT2B on AEC and of 5HT2C as a major receptor subtype on AM. In freshly isolated AM, 5-HT (10 nM, 10 µM) induced a rapid rise in [Ca2+]i followed by a sustained increase. The presence of extracellular Ca2+ was required for the sustained [Ca2+]i elevation, but not for the acute increase. The 5-HT-induced increase in [Ca2+]i was not observed in 5HT2C-deficient AM and in wild-type AM treated with a low dose of the 5HT2C-selective inhibitor RS102221. AM, as well as AEC stimulated with 10 µM 5-HT for 24 h increased production of CCL2 as indicated by ELISA for AEC and dot-blot assay and ELISA for AM.
These data demonstrate the presence of functional 5HT2C receptors on AM and identify 5-HT as a novel modulator of chemokine production in AM and AEC.

Funded by: DFG, IntGK 1062, Z. Mikulski and Z. Zaslona contributed equally to the study

Kategorie: Lecture

Rubrik: 1.Main Topic I
Abstract Nr.:10

Titel:Intravital observation of antigen transport by intestinal M cells - a 3d time lapse study in mice

Autoren: Gebert A.(1),Blessenohl M.(1),Schueht A.(1),Orzekowsky R.(2),Huettmann G.(2),Klinger A.(1),

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Abstract:
In the dome epithelium of the Peyer's patches, specialized epithelial cells (M cells) steadily sample antigenic matter from the gut lumen. The M cells transport it across their cytoplasm and bring it into contact with lymphocytes hosted in a pocket-like invagination of the M cell's basolateral membrane. Until now, knowledge on M cells is derived from histology of fixed tissue, but data about the true intravital situation are lacking. In a novel experimental setup based on 2-photon microscopy, we markerless identified intestinal M cells in living, anaesthetized mice, as they possessed a less regular structure of their mitochondria than enterocytes. Most of the M cells observed were in close contact to clusters of vigorously moving lymphocytes. Time lapse recordings showed that the organelles contained in the cytoplasm of M cells were in a continuous motion which probably reflects the movement of transcytotic vesicles. To observe the antigen transport, we applied a mouse M cell marker, the Ulex europaeus agglutinin (UEA-I-FITC), onto the living gut mucosa. It specifically bound to the apical membrane of the M cells and was endocytosed within less than 5 min. 3D timer lapse series recorded over more than 3 hrs revealed that tracer-containing vesicles in M cells moved at a speed of 1.85±0.47 microns/min. The resulting net transport speed from the apical membrane towards the basal parts of the M cells was 0.68±0.15 microns/min. The results show that our novel setup allows immunological processes to be observed in the living organism at a sub-micron resolution.

Kategorie: Lecture

Rubrik: 7.Neuroimmunology
Abstract Nr.:11

Titel:Somatostatin modulates mast cell-induced responses in murine spinal neurons

Autoren: Van Op den bosch J.(1),Van Nassauw L.(2),Van Marck E.(3),Timmermans J.-P.(1),

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Abstract:
Intestinal inflammatory responses are coordinated by the extensive bidirectional communication between enteric neurons and mast cells embedded within the intestinal wall. The expression of multiple somatostatin receptor (SSTR) subtypes in mucosal mast cells and in the extrinsic and intrinsic nerve fibres, suggests that somatostatin (SOM) is able to modulate the inflammatory activities of both neurons and mast cells. Therefore, we assessed the modulatory effects of SOM on the short-term and long-term effects induced by the main mast cell mediators histamine (HIS) and 5-HT on murine spinal neurons. HIS and 5-HT induced neuronal CGRP release and calcium-mediated activation of neurons and non-neuronal cells. Both of these mast cell-induced effects were strongly reduced by preincubating the spinal cultures with SOM. Moreover, qPCR and quantitative analysis revealed a profound inhibitory effect of SOM on the increased neuronal expression of substance P, CGRP and SOM induced by long-term exposure to HIS and 5-HT. Immunocytochemical and molecular-biological experiments suggest the involvement of somatostatin receptor 1 (SSTR1) and SSTR2A in these SOM-dependent effects. Moreover, intestinal inflammation was accompanied not only by increased numbers of spinal neuronal somata expressing substance P and CGRP, but also by enhanced expression levels of SOM, SSTR1, SSTR2A and SSTR4 in spinal ganglia. These data reveal that intestinal inflammation induces the onset of both pro-inflammatory cascades and endogenous systems destined to prevent excessive tissue damage. These data provide for the first time functional evidence that SOM is able to directly modulate intestinal inflammatory responses by interference with the mast cell-neuron communication.

Kategorie: Lecture

Rubrik: 7.Neuroimmunology
Abstract Nr.:12

Titel:In MP4-induced EAE of C57BL/6 mice functional deficits correlate with structural CNS damage

Autoren: Kuerten S.(1),Laurentius L.(1),Gruppe T.(1),Lehmann P.(2),Addicks K.(1),

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Abstract:
While EAE is widely accepted as animal model for MS, the major criticism has remained that none of the presently available models entails a clear correlation between functional and structural damage, making it difficult to systematically evaluate the success of different treatment options. C57BL/6 mice were immunized with the MBP-PLP fusion protein MP4. Lesion frequencies and sizes were evaluated by HE staining, lesion composition by immunohistochemistry. Demyelination and axonal damage were assessed by LFB and SMI-32/SMI-99 staining in addition to the evaluation of semi-thin sections.
MP4-induced EAE was characterized by a differential targeting of CNS regions allowing a clear distinction between the acute and chronic stage of the disease. This distinction was further underlined by the dynamics of lesion composition. While in acute EAE CD4+ T cells and macrophages prevailed, in chronic EAE B cell follicules were predominant. It has been shown before that the presence of B cell follicules was correlated with MS onset and progression. Thus, the MP4 model may facilitate our understanding of how different cell subsets can mediate disease severity. Moreover, lesion frequencies and sizes in addition to the patterns of demyelination and axonal loss showed an excellent correlation with the clinical score further underlining the suitability of this model for function-based studies.
MP4-induced EAE is a unique model with a strong correlation between CNS pathology and clinical disability. This model will fuel our understanding of how neuroanatomical correlates of the disease can mediate functional deficits.

Kategorie: Lecture

Rubrik: 7.Neuroimmunology
Abstract Nr.:13

Titel:Reporter gene-expressing bone marrow-derived stromal cells are immune-tolerated following implantation in the central nervous system of syngeneic immunocompetent mice.

Autoren: Bergwerf I.(1),De Vocht N.(2),Tambuyzer B.(1),Verschueren J.(3),Reekmans K.(1),Daans J.(1),Ibrahimi A.(4),Van Tendeloo V.(5),Chatterjee S.(6),Goossens H.(7),Jorens P.(8),Baekelandt V.(9),Ysebaert D.(10),Van Marck E.(6),Berneman Z.(5),Van Der Linden A.(3),Ponsaerts P.(5),

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Abstract:
In many pre-clinical cell therapy studies, imaging of cellular implants in the CNS and potential reporter gene and cell-based immunogenicity,remain challenging research topics.
In this study, we performed cell implantation experiments in the CNS of immunocompetent mice using autologous luciferase-expressing bone marrow-derived stromal cells (BMSC-Luc) cultured from ROSA26-L-S-L-Luciferase transgenic mice, and BMSC-Luc genetically modified using a lentivirus encoding the enhanced green fluorescence protein (eGFP) and the puromycin resistance gene (Pac) (BMSC-Luc/eGFP/Pac).Both reporter gene-modified BMSC populations displayed high engraftment capacity in the CNS of immunocompetent mice, despite potential immunogenicity of introduced reporter proteins, demonstrated by real-time bioluminescence imaging (BLI) and histological analysis at different time-points post-implantation. In contrast, both BMSC-Luc and BMSC-Luc/eGFP/Pac did not survive upon intramuscular cell implantation, as demonstrated by real-time BLI at different time-points post-implantation. In addition, ELISPOT analysis demonstrated induction of IFN-gamma-producing CD8+ T-cells upon intramuscular cell implantation, but not upon intracerebral cell implantation, indicating that BMSC-Luc and BMSC-Luc/eGFP/Pac are immune-tolerated in the CNS. However, in our experimental transplantation model, results also indicated that reporter gene-specific immune-reactive T-cell responses were not the main contributors to the immunological rejection of BMSC-Luc or BMSC-Luc/eGFP/Pac upon intramuscular cell implantation.
We demonstrate that reporter gene-modified BMSC derived from ROSA26-L-S-L-Luciferase mice are immune-tolerated upon implantation in the CNS of syngeneic immunocompetent mice, providing a research model for studying survival and localisation of autologous BMSC implants in the CNS by real-time BLI and histological analysis in the absence of immunosuppressive therapy.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:14

Titel:The cuprizone model as tool for studying demyelination in multiple sclerosis

Autoren: Kipp M.(1),Clarner T.(1),Groebe A.(1),Beyer C.(1),

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Abstract:
Advances in multiple sclerosis research have been made as a consequence of the use of adequate animal models. The cuprizone-feeding model is suitable for studying toxic demyelination and reflects a specific histological subtype of multiple sclerosis (type III lesions). During multiple sclerosis, different brain structures are affected and several symptoms observed. Dissemination in space in cuprizone-induced demyelination and regional pathological differences are only poorly understood. This study characterizes local demyelination processes and cellular pathologies in different adult brain areas including white and grey matter structures.
Mice were fed cuprizone for up to 13 weeks. The myelin status was analyzed by histological stainings, electron microscopy, and immunohistochemistry for oligodendroglia, astroglia, and microglia markers in the telencephalon, hippocampus, and cerebellum.
White and grey matter tracts were equally affected by cuprizone but regional diversity in demyelination was detected. Demyelination in the hippocampus was pronounced in a subset of white and gray matter areas. The cortical and subcortical grey matter was damaged in the telencephalon, whereas only the subcortical grey matter was injured in the cerebellum. Additionally, we observed hypertrophic and hyperplastic astrocytosis accompanied by microglia invasion in demyelinated brain regions.
The cuprizone model correlates well with recent histopathological data from human multiple sclerosis. This model may serve as a valuable tool for studying de- and remyelination in the brain and offers the opportunity to better characterize the underlying molecular processes of regional pathology.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:15

Titel:Expression of the clock genes AMPHIPER and AMPHIBMAL in the lancelet *Branchiostoma lanceolatum*

Autoren: Schomerus C.(1),Laedtke E.(1),Korf H.(1),Wicht H.(1),

Adressen:(1)Dr. Senckenbergische Anatomie, Institut für Anatomie II|Klinikum der Goethe-Universität Frankfurt/Main|Frankfurt|Germany; email:schomerus@em.uni-frankfurt.de

Abstract:
Recently, we presented first data on the organization the circadian system of a lancelet, Branchiostoma lanceolatum, a close invertebrate relative of vertebrates. Branchiostoma was found to display rhythmic locomotor activity which persisted under constant darkness, suggesting the presence of a self-sustained circadian oscillator. Such oscillators are characterized by the expression of so-called clock genes. We cloned one of these genes (amphiPer) and localized its expression in a restricted region of the anterior neural tube, termed the anterolateral periventricular (alp) cell group. Here we expanded our observations by showing that amphiPer expression is clearly circadian. Also under constant darkness, the amphiPer mRNA levels fluctuated in a rhythmic manner, with peak levels in the early subjective day. Furthermore, we cloned another clock gene, namely amphiBmal. In a phylogenetic analysis of the amino acid sequence, AMPHIBMAL clearly grouped with the sequences of BMALs from other deuterostomes. In fact, its sequence is very similar to the presumed ancestral sequence which gave rise to the Bmal paralogs (1-3) of craniates. Using in situ hybridization we analyzed the expression pattern of amphiBmal. It was shown to colocalize with amphiPer in the anterior neural tube. A densitometric analysis of in situ hybridized sections revealed a significant increase of the staining intensity in the dark phase. These data support our hypothesis that the alp cell group may harbour the circadian oscillator and may thus be homologous to the suprachiasmatic nucleus of craniates.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:16

Titel:Enhanced fibroblast growth factor receptor signaling promotes adult axon growth

Autoren: Hausott B.(1),Vallant N.(1),Klimaschewski L.(1),

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Abstract:
Fibroblast growth factors (FGF) play a prominent role in axon growth. They activate 4 types of FGF receptors (FGFR1-4). FGFR1, -2 and -4 are expressed in adult sensory neurons obtained from dorsal root ganglia (DRGs). In response to FGFR activation, the Ras/Raf/ERK (extracellular signal-regulated kinase) and the PI3K (phosphatidylinositol-3 kinase)/Akt pathway mediate different modes of axonal growth. The Ras/Raf/ERK kinase pathway is attenuated by Sprouty proteins, which represent a major group of negative feedback inhibitors. Mammals exhibit four Sprouty isoforms (Sprouty1-4). Termination of the signal is achieved by the ubiquitin ligase c-Cbl which tags the receptor with ubiquitin for endocytosis and lysosomal degradation.
We analyzed the effects of FGFR1-overexpression, lysosomal inhibition of receptor degradation and down-regulation of Sprouty negative feedback inhibitors on axon growth by adult sensory neurons. FGF-2 induced activation of ERK and promoted elongative axon growth in response to a preconditioning sciatic nerve lesion. FGFR1 overexpression enhanced FGF-2-induced axon growth which was further increased by lysosomal inhibition of receptor degradation. The negative feedback inhibitors Sprouty1, -2 and -4 are all expressed in adult sensory neurons. Sprouty2 revealed the highest expression and Sprouty1 and -4 were up-regulated in response to FGF-2 treatment. Knockdown of Sprouty2 strongly enhanced FGF-2-induced elongative axon growth and activation of ERK and Ras, whereas knockdown of Sprouty1 and -4 had no effect on axon growth. Taken together, our results indicate that enhanced FGFR signaling promotes axon regeneration in vitro.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:17

Titel:The mammalian molecular clockwork controls rhythmic expression of the ryanodine receptor

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Abstract:
The core molecular clockwork in the suprachiasmatic nucleus (SCN) is based on autoregulatory feedback loops of transcriptional activators (CLOCK/NPAS2 and BMAL1) and inhibitors (mPER1-2 and mCRY1-2). In order to synchronize the phase of the molecular clockwork to the environmental day and night condition, light at dusk and dawn increases mPer expression. However, the signal transduction pathways differ remarkably between the day/night and the night/day transition. Light during early night leads to intracellular Ca2+ release by neuronal ryanodine receptors (RyRs) resulting in phase delays. Light during late night triggers an increase in guanylyl cyclase activity resulting in phase advances. To date, it is still unknown how the core molecular clockwork regulates the availability of the respective input pathway components. Therefore, we examined the light resetting mechanism in mice with an impaired molecular clockwork (BMAL1-/-) using in situ hybridization, real time PCR, immunohistochemistry, transcription assays and calcium imaging (2 photon microscopy). We found that in BMAL1-/- mice light–induced mPer expression was selectively impaired during early night. Ryr mRNA and RyR protein levels were dramatically reduced in the SCN of BMAL1-/- mice and transcriptional activity of the Ryr promoter could be controlled by molecular clockwork components. Furthermore, calcium imaging showed that the responsiveness of SCN cells of BMAL1-/- mice towards the RyR-agonist caffeine was drastically reduced. In summary, our findings provide the first evidence that the mammalian molecular clockwork controls Ryr expression and thus its own photic input pathway components. Supported by the DFG (GA737/2-3).

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:18

Titel:Release of a neuroprotective factor from Spraque-Dawley hippocampus promotes survival of BDV-infected dentate granule cells of Lewis rats in vitro

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Abstract:
In the hippocampus of Borna disease virus (BDV)-infected newborn Lewis rats, dentate granule cells undergo progressive neuronal death. In contrast, dentate granule cells from Spraque-Dawley (SD) rats appeared to persist after BDV infection. These rat strain specific differences are retained in BDV-infected hippocampal slice cultures. Here we tested if hippocampal tissue from Spraque-Dawley strain can exert a neuroprotective effect on BDV-infected dentate granule cells from Lewis rats in vitro.
We performed various combinations of co-cultures (Lewis hippocampus + SD dentate gyrus; Lewis dentate gyrus + SD hippocampus and distantly placed hippocampi of either strain). Slice cultures were infected with BDV, incubated up to 4 weeks and immunostained against calbindin and viral protein N.
BDV-infected hippocampus/dentate gyrus co-cultures of both mixed rat strains and SD rats revealed maintenance of the dentate gyrus and mossy fiber projections whereas co-cultures composed only from Lewis rats showed massive granule cell loss. In infected hippocampal cultures of both rat strains that have been cultivated distant from each other but in the same dish the granule cell layer of Lewis rat hippocampus remained intact.
Based on these observations we conclude the existence of a soluble factor released by SD hippocampal tissue which has a protective potential against dentate granule cell death in Lewis rats.
(Supported by the DFG: He 1520, SCHW 632).

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:19

Titel:How to explain estrus cyclicity of neurogenesis in the hippocampus?

Autoren: Fester L.(1),Hannig J.(1),Jarry H.(2),Rune G.(1),Prange-Kiel J.(3),

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Abstract:
Ovarian estrogens have been demonstrated to influence neurogenesis, as evidenced by estrous cyclicity of proliferation in the dentate gyrus (Tanapat et al., 1999; 2005). In previous experiments, we have shown that neurogenesis in hippocampal cultures requires local estradiol synthesis, whereas application of estradiol to the cultures was ineffective (Fester et al., 2006). This discrepancy prompted us to study GnRH as a potential regulator of hippocampal estradiol synthesis and proliferation, in view of abundant gonadotropin-releasing hormone receptor (GnRH-R) mRNA expression in the hippocampus and the direct effect of GnRH on estradiol synthesis in gonadal cells. In hippocampal cultures, we measured the release of 17ß-estradiol into the medium and counted granule cells, which were positive of Ki67, a reliable proliferation marker, in response to various doses of GnRH. Estradiol synthesis and the number of Ki67 positive cells consistently increased in a dose-dependent manner at low doses of GnRH but decreased to control levels at higher doses. GnRH was ineffective in the presence of GnRH antagonists or aromatase inhibitors. Since GnRH-R expression was five-fold higher in the hippocampus compared to the cortex, our data strongly suggest that estrus cyclic neurogenesis in the female hippocampus results from cyclic release of GnRH.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:20

Titel:Identification of an endocannabinoid system in the hypophysial pars tuberalis of the syrian hamster, a photoperiodic species

Autoren: Yasuo S.(1),Koch M.(1),Schmidt H.(2),Ziebell S.(2),Geisslinger G.(2),Korf H.(1),

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Abstract:
The pars tuberalis (PT) represents the rostral extension of the adenohypophysis and is attached to the median eminence and the hypophysial portal vasculature. Due to this location the PT is considered to play multiple roles for neuroendocrine mechanisms within the hypothalamo-hypophysial system. The PT is the primary target for the melatonin signal which is secreted from the pineal gland and transmits photoperiodic information, and the PT plays an essential role for the seasonal regulation of gonadotropic and lactotropic axes. However, the factors through which the PT affects the hormonal secretion from the hypophysial pars distalis (PD) are not yet identified. Several data suggest the involvement of endocannabinoids (e.g. anandamide and 2-arachidonoylglycerol, 2-AG) in neuroendocrine regulation, although it remains unclear where and how they elicit their effects. In this study, we demonstrated the expression of virtually all components of an endocannabinoid system in the PT of the Syrian hamster, a photoperiodic species. These include N-acylphosphatidylethanolamide-phospholipase D and diacylglycerol lipase alpha/beta, synthesizing enzymes for anandamide and 2-AG, respectively, fatty acid amide hydrolase and monoacylglycerol lipase, metabolizing enzymes for anandamide/2-AG and 2-AG, respectively. Immunohistochemical investigation confirmed the localization of these enzymes in the PT. The cannabinoid receptor 1 is expressed in the PD and several endocannabinoids including anandamide and 2-AG were detected by liquid chromatography tandem mass spectrometry. These results suggest that endocannabinoids are important signals from the PT which are involved in seasonal regulation of neuroendocrine functions.

Supported by LOEWE Lipid Signaling Forschungszentrum Frankfurt (LiFF) and Alfred und Gertrud Kassel-Stiftung

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:21

Titel:Quantitative characterization of alveolar epithelial type II cells and lamellar bodies in the human lung by stereology and electron tomography

Autoren: Vanhecke D.(1),Widmer C.(1),Haenni B.(1),Wahlers T.(2),Nyengaard J.(3),Gundersen H.(3),Ochs M.(1),

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Abstract:
A surface active agent known as alveolar surfactant covers the respiratory epithelium of the lung. It is produced by type II alveolar epithelial cells in specific vesicles known as lamellar bodies (LB) and released upon mechanical stretching of the alveolus. Surfactant secretion is a slow process and is regulated at post-fusion level: the fusion pore of the lamellar body with the plasma membrane forms a structural barrier for secretion. The contradiction of the slow secretion process with the quick demand for surfactant during inspiration led to the postulation of an intermediate surfactant pool that should be immediately available for release.
Five human lungs were analyzed. We occasionally observed that LB fuse but maintain surrounded by one membrane (the limiting membrane). The interface between such adjacent LB was defined as the LB-LB pore. These fused LB differ significantly from single LB, but not from those LB in the process of secretion, on several morphometric parameters. This indicates that these fused LB represent a matured subpopulation.
Taken together, three subpopulations could be defined in the LB of the human alveolar epithelial type II cell. The small immature LB, the larger matured LB with an LB-LB pore and the LB in the process of secretion fused with the plasma membrane. The matured LB, with an LB-LB pore, therefore represent the intermediate surfactant pool with access to the alveolar lumen via an already existing fusion pore. Thereby, sufficient amounts of surfactant can be released upon mechanical stretching.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:22

Titel:Impaired cAMP and Rac 1 signalling cause TNF-alpha-induced endothelial barrier breakdown in microvascular endothelium

Autoren: Schlegel N.(1),Waschke J.(1),

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Abstract:
Tumor necrosis factor-alpha (TNF-alpha) contributes to endothelial barrier breakdown in septic inflammation. The critical involvement of Rho A/Rho kinase signalling in this respect has recently been challenged. In the present study we tested whether impaired cAMP and Rac 1 signalling contribute to endothelial barrier breakdown. We demonstrate that TNF-alpha in human dermal microvascular endothelial cells (HDMECs) disrupts endothelial barrier properties within 75min as revealed by measurements of transendothelial electrical resistance (TER) and of 70kD FITC-dextran flux. This was associated with the formation of intercellular gaps, stress fibers and fragmentation of VE-cadherin and claudin 5 immunostaining. Under these conditions, Rho A activity was significantly increased whereas Rac 1 activity was decreased and Cdc42 was unaltered. Rho kinase inhibition using Y27632 did not prevent TNF-alpha-induced barrier breakdown. In contrast, preincubation with forskolin and rolipram (F/R) to increase cAMP abolished all TNF-alpha-induced effects. Moreover, we detected that cAMP levels were dramatically reduced to 38 ± 12% of controls in response to TNF-alpha. Inactivation of Rac 1 but not Rho A was completely blocked by F/R-mediated increase of cAMP. In summary, our data indicate that TNF-alpha-induced endothelial barrier disruption in part is caused by cAMP-dependent Rac 1 inactivation rather than by activation of Rho A.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:23

Titel:Line-1 mediated retrotransposition events influence endothelial but not epithelial cell proliferation

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Abstract:
Long interspersed nuclear element-1 (LINE-1) retrotransposons are mobile elements that insert into new genomic locations via reverse transcription of an RNA intermediate. LINE-1 plays a significant role in shaping of the mammalian genome, and is an active component involved in controlling cell differentiation and proliferation. LINE-1 retrotransposons have known implications in origin and progression of tumors by either causing insertional mutations or chromosomal translocations/rearrangements.
The aim of this study is to analyse the effect of LINE-1 mediated retrotransposition events on endothelial and epithelial cell proliferation. This study was assessed in the porcine aortic endothelial (PAE) cell line, the human epithelial bladder cancer (RT4) cells and in the epithelial lung carcinoma (A549) cells.
The cell proliferation and migration was significantly down-regulated in endothelial cell clones with retrotransposition events as compared to the analysed epithelial cell clones. Also the determination of the cell cycle status of the generated cell clones by FACS analysis indicates a G0/G1 stage arrest in the PAE cell clones as compared to the epithelial cell clones RT4 and A549. Interestingly, the proliferation activity of PAE cell clones with retrotransposition events return to the proliferation level of untransfected wild type PAE's after culturing and splitting for several times.
Taken together, our data show that only active LINE-1 retrotransposition events result in decreased endothelial cell proliferation and migration in vitro. Thus, the presence of LINE-1 encoded proteins in human vascular endothelial cells, as shown previously, and the hereby mediated potential retrotransposition events may have relevance for angiogenesis.

Kategorie: Lecture

Abstract Nr.:24

Titel:Cyclic tandem peptides targeting VE-cadherin transinteraction stabilize endothelial barrier function

Autoren: Efthymiadis A.(1),Heupel WM.(1),Schlegel N.(1),Müller T.(2),Baumer Y.(1),Baumgartner W.(3),Drenckhahn D.(1),Waschke J.(1),

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Abstract:
Inflammatory stimuli result in vascular leakage with potentially life threatening consequences. As a key barrier component, loss of vascular endothelial (VE-) cadherin-mediated adhesion often precedes endothelial breakdown. This study aimed to stabilize VE-cadherin transinteraction and endothelial barrier function using peptides targeting the VE-cadherin adhesive interface. After modeling the transinteracting VE-cadherin structure, an inhibiting single peptide (SP) against a VE-cadherin binding pocket was selected, which specifically blocked VE-cadherin transinteraction as analyzed by single molecule atomic force microscopy (AFM). The tandem peptide (TP) consisting of two SP sequences in tandem was designed to strengthen VE-cadherin adhesion by simultaneously binding and cross-bridging two interacting cadherin molecules. Indeed, in AFM experiments TP specifically rendered VE-cadherin transinteraction resistant against an inhibitory monoclonal antibody. Moreover, TP reduced VE-cadherin lateral mobility and enhanced binding of VE-cadherin-coated microbeads to cultured endothelial cells, but acted independent of the actin cytoskeleton. TP also stabilized endothelial barrier properties against the Ca2+ ionophore A23187 and the inhibitory antibody. Finally, TP abolished endothelial permeability increase induced by tumor necrosis factor-alpha in microperfused venules in vivo. Stabilization of VE-cadherin adhesion by cross-bridging peptides may therefore be a novel therapeutic approach for the treatment of vascular hyperpermeability.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:25

Titel:TGFBI inhibits proliferation and invasion of neuroblastoma by MYCN-independent up regulation of TFPI2

Autoren: Becker J.(1),Wilting J.(1),

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Abstract:
Neuroblastoma (NB) is the most common solid tumour in infants. Approximately 40 % of the affected children die in spite of aggressive multimodal therapy. Amplification of the MYCN is the most prominent adverse prognostic marker in NB and correlates with fast growing, highly invasive tumours. We sought to study the effects of TGFBI (transforming growth factor beta induced, BIGH3, keratoepithelin) expression on neuroblastoma.
We used micro-arrays and real-time RT-PCR to evaluate expression levels of MYCN, TGFBI and TFPI2 (tissue factor pathway inhibitor 2, PP5, MSPI) on primary tumour samples and cell lines. TGFBI over-expressing cell lines were established and characterized in vitro and in vivo.
We have shown that enhanced TGFBI expression in human neuroblastoma cells inhibits proliferation and invasion in vitro and in vivo. Additionally, TFPI2, a potent inhibitor of matrix-metalloproteinases (MMPs), was found most prominently up regulated in TGFBI transfected cells. While both TGFBI and TFPI2 expression inversely correlate with MYCN expression, TGFBI transfected cells with high MYCN expression show a dose-dependent increase in TFPI2 transcripts with no alterations in the MYCN status.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.26

Titel:Desmocollin 3-mediated binding is crucial for keratinocyte cohesion and epidermal integrity

Autoren: Spindler V.(1),Heupel W.(1),Khan S.(1),Drenckhahn D.(1),Waschke J.(1),

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Abstract:
Desmocollin (Dsc) 1-3 and desmoglein (Dsg) 1-4, transmembrane proteins of the cadherin family, form the adhesive core of desmosomes. Recently, conditional Dsc 3 deficiency was demonstrated to lead to lethal epidermal blistering in mice. In this study, we therefore investigated the role of homo- and heterophilic interactions of Dsc 3 for keratinocyte cohesion. Atomic force microscopy revealed homophilic trans-interaction of Dsc 3 and heterophilic interaction of Dsc 3 with Dsg 1 on a single molecule level. However, no evidence for heterophilic binding of Dsc 3 to Dsg 3 was detected. Furthermore, blocking Dsc 3 function with a monoclonal antibody targeting the extracellular domain induced intraepidermal blisters in an ex vivo model of human skin. As probed by dissociation assays, this Dsc 3 antibody caused loss of intercellular adhesion in monolayers of cultured human keratinocytes. The efficiency exceeded that of AK23, a monoclonal antibody directed against Dsg 3. Similarly, laser tweezer experiments in keratinocyte cultures showed loss of Dsc 3-mediated adhesion as a result of treatment with the Dsc 3-directed antibody. Taken together, our data provide new insights into the interaction of desmosomal cadherins and indicate a pivotal role for Dsc 3 in maintaining epidermal integrity.

Kategorie: Lecture

Rubrik: 9.Developmental Biology
Abstract Nr.:28

Titel:Form variants of the proximal end of the caput longum of the biceps brachii:

Autoren: Dierickx C.(1),Ceccarelli E.(2),Conti M.(2),Vanlommel J.(1),Castagna A.(2)

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Abstract:
The intra-articular part of the caput longum of the biceps brachii (LHB) tendon usually runs free, but a number of variations of fusions with the capsule are possible.
By taking into account the current knowledge of the embryology of the LHB and also a large literature review including some very old theories, even with comparative animal studies, we demonstrate the variability of the intra-articular portion of the LHB.
All these variations refer to the human embryological evolution of the LHB which migrates from extra- to intra-articularly after the fourth month. This process may apparently stop prematurely, which results in one of the following conditions: a partial or complete mesothenon between biceps and capsule, a pulley-like sling, an intracapsular or an extracapsular arranged or adherent biceps tendon, a double tendon origin, a reversed-type split-tendon or even complete absence of the tendon. We illustrate all these variants with arthroscopic pictures and video recordings of patients of our own practice. The incidence of these variants and their associated pathologies are investigated.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:40

Titel:Vital microscopic morphometry applied to the heart of hen's embryo in reference to early function of the endocardial cushion

Autoren: Palubinskiene J.(1),Kipp M.(2),Valanciute A.(1),Salomskaite-Davalgiene S.(1),Graf von Keyserlingk D.(3),

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Abstract:
In its very early development the heart is a stretched fluid filled tube with openings at both ends. The fluid is expelled by contraction of the wall of the tube. The fluid leaves the tube, but only through one of the openings. The question is: which mechanical conditions are responsible for that? Measurements of intracardial pressure are not available, but the volume of the different parts of the heart, when in action, may be registered quantitatively by vital microscopic morphometry. Shoots of single phases of the heart actions from video recordings were plotted and evaluated. These data were compared with measurements of structures of the embryonic heart from serial sections slices cut in right angle to the vital observation. In the early stage the endocardial cushion, which can be seen also in the living state, covers the inner wall of the heart from the transition of the atrium to the ventricle, as well as part of the ventricle and the truncus arteriosus to different degree. The endocardial cushion smoothes and narrows the lumen of those parts of the heart, which are stressed by higher speed blood flow. This plastic connective tissue seems to have even in very early development a function, and not only, as is well known, in later phases, when it takes part in partitioning the atrio-ventricular canal and in the formation of the connective tissue frame-work of the cardiac valves.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:41

Titel:Intussusceptive angiogenesis contributes to tumor escape and recovery after anti VEGF treatment and ionizing radiation

Autoren: Djonov V.(1),

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Abstract:
Inhibitors of angiogenesis and radiation induce compensatory changes in the tumor vasculatur.
To assess the response to the treatment, the tumors were analyzed during the recovery phase.
Mammary carcinoma allografts were investigated by vascular casting, electron, light, confocal microscopy and immunoblotting after fractionated irradiation or treatment with the VEGF-receptor tyrosine kinase inhibitor, PTK787/ZK222854.
Both treatments had similar effects on the tumor vasculature. They reduced the tumor vascularization, particularly in the tumor medulla. After cessation of therapy, the tumor vasculature expanded predominantly by intussusception with a plexus composed of enlarged sinusoidal-like vessels containing multiple transluminal tissue pillars. Tumor revascularization originated from preserved SMA-positive vessels in tumor cortex. Quantification revealed that recovery was characterized by an angiogenic switch from sprouting to intussusception. The upregulated SMA-expression during the recovery reflected the recruitment of SMA-positive cells for intussusception as a part of angioadaptive mechanism. Tumor recovery was associated with a dramatic decrease (by 30-40%) in the intratumoral microvascular density, probably as result of intussusceptive pruning, surprisingly with only a minimal reduction of the total microvascular (exchange) area. Therefore, the vascular supply to the tumor was not severely compromised as demonstrated by HIF-1-alpha expression.
Irradiation and anti-angiogenic therapy causes a switch from sprouting to intussusceptive angiogenesis as part of a compensatory response to preserve and restore perfusion. Intussusceptive angiogenesis with an associated low endothelial proliferation rate and permeability, may represent an escape mechanism and account for development of resistance to therapy, as well as the rapid recovery of tumor vasculature after cessation of therapy.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:42

Titel:Primary ring of ventricular conduction system and effect of hemodynamic loading upon its function

Autoren: Sedmera D.(1),Sebestova B.(1),Machalek J.(1),

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Abstract:
Primary ring represents specialized conduction tissues in the early ventricular myocardium, and connects to the atrioventricular canal. It has been originally identified immunohistochemically and as a region of slowed proliferation. Later studies have shown that it participates in spreading of ventricular activation during stages preceding ventricular septation in the chick and rat. Here we assessed its presence using optical mapping in the mouse embryos between ED9.5-13.5 and chicks between ED3-ED5, and tested the effects of mechanical unloading in organ culture setup upon its function.
In E3 and E4 chick embryos cultured without hemodynamic loading for 24 h, we observed a significant decrease in percentage of hearts with primary ring conduction pathway assessed by optical mapping. Preferential activation pathway utilizing the primary ring or activation from apex to base was dominant in freshly isolated mouse embryonic hearts between ED9.5 and ED11.5, while in hearts cultured for 24 hours occurred a regression in normal developmental timeline with appearance of ventricular activation patterns from base to apex. We thus conclude that appropriate mechanical loading is essential during the early phases of conduction system formation and maturation.

Supported by MFM VZ 0021620806 and GACR 304/08/0915.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:43

Titel:Chicken's heart in early development forms structures even distant

Autoren: Balnyte I.(1),Prescher A.(2),Valanciute A.(1),Graf von Keyserlinkgk D.(1),

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Abstract:
The embryo starts to change its external form dramatically at about 33 hours of hen's egg incubation (10 somites stage, HH 10). The embryo separates from the blastoderm, it cranial part turns from a prone to a lateral position. At the same time the fore-brain is bent at right angles to the axis of the embryo (cranial flexure). This happens when the heart starts beating. The ventricle becomes dilated and it bents out of the midline to the embryos right. The heart elongates and gets its U-shape. By means of vital microscopic morphometry it was examined whether a correspondence between these mentioned events perhaps in a kind of causal connection exists. Small glass windows were installed on top of the eggs. The eggs were kept in an incubator with transparent roof so that continuous observation and filming of the developing embryo with a stereomicroscope under constant viewpoint was possible. Measurements in the depth of the subject were done by optical focusing; the turning of the driving gear was enlarged by a laser beam. In the horizontal plane distances were measured by a Zeiss optical device. Video sequences were used to verify the heart action, especially under the question of direction of hearts beat in regard to shape changes of the embryo. Indications were gained that heart takes active part in the change of the external form of the embryo at this phase of development.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.: 44

Titel:Endothelial and epithelial characterization of CD26 in prostate cancer tissues

Autoren: Frindte J.N.(1),Scheffrahn I.(1),Schmid K.(2),Reutter W.(3),Ergün S.(1),Singer B.B.(1),

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Abstract:
CD26, a serine protease, is involved in multiple physiological processes including cell differentiation and tumor growth. The aim of this study was to evaluate the expression of CD26 in vascular endothelial (VECs), lymphendothelial (LECs) and epithelial cells in prostate cancer tissue. The expression of CD26 in VECs (HUVECs and HDMECs) and LECs was studied by FACScan. Immunofluorescence studies were performed for CD26, CD31, Podoplanin and Prox1 on HDMECs. Immunohistochemical analyses on paraffin sections of human prostate were performed to determine the localization pattern of CD26.
FACScan analyses demonstrated that HDMECs but not HUVECs expressed CD26 on their surface. Detailed studies on HDMECs which are composed by VECs and LECs revealed that both, cultured LECs as well as VECs are positive for CD26 as confirmed by double staining for podoplanin. Immunofluorescence studies on cultured HDMECs revealed CD26 negative and positive cells. In a part of these cells CD26 was co-localized with CD31. Immunohistochemical staining for CD26 on different stages (Gleason score) of prostate cancer tissues revealed a heterogeneous expression pattern. In all tumor stages CD26 was present in endothelial cells of lymphatics and veins, but not in those of arteries.
Our results show, that the expression of CD26 in epithelial cells is related to prostate cancer stage, while its expression in lymphatics and veins is not related. Our data show, that CD26 is not an exclusive marker for lymphatics, rather for both, lymphatics and veins and may therefore help to distinguish arterial from venous endothelial cells.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:45

Titel: In vivo imaging of the cyclic changes in cross-sectional shape of the ventricular region of pulsating embryonic heart tubes from the initial phase of ventricular trabeculation.

Autoren: Männer J(1)(2),Thrane L(3),Norozi K(4),Mesud Yelbuz T(4)

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Abstract:
The early embryonic heart is a valveless tube that is said to generate unidirectional blood flow by peristaltoid contractions. The cyclic deformations of pulsating embryonic heart tubes were traditionally described as concentric narrowing and widening of a tube of circular cross-section. Using real-time high-resolution optical coherence tomography, we have recently shown that the cyclic deformations of pulsating embryonic heart tubes run other than traditionally thought (Männer et al., 2008, Dev Dyn. 237:953-61). During the cardiac cycle, only the myocardial tube undergoes concentric narrowing and widening while the endocardial tube undergoes eccentric narrowing and widening, having an elliptic cross-section at end-diastole and a slit-shaped cross-section at end-systole. The eccentric deformation of the endocardial tube leads to complete occlusion of its lumen at end-systole (100%! ejection fraction) and is the consequence of an uneven distribution of extracellular matrix (cardiac jelly) between the myocardium and endocardium. Due to technical limitations, our previous analyses were confined to relatively early stages of ventricular development (chick embryos, HH-stages 10-13). We now have documented the cyclic changes in cross-sectional shape of the ventricular bend of heart tubes from the initial phase of trabeculation (HH-stages 14-17), which is characterized by the disappearance of a large amount of cardiac jelly in the ventricular region. We have found that the cardiac jelly is preferentially removed at the outer curvature of the ventricular bend due to centrifugal outgrowth of endocardial pockets and furrows along cardiac jelly fibrils. The end-diastolic lumen of the ventricular endocardial tube thereby changes its cross-sectional shape from an elliptic (HH-stages □14) into a bell-shaped figure (HH-stages 15-17). During systole, the bell-shaped endocardial tube becomes compressed like a bellow so that its lumen is almost completely occluded at end-systole.

Kategorie: Lecture

Rubrik: 2.Main Topic II
Abstract Nr.:46

Titel:Angiogenesis in hyperplastic endometrium

Autoren: Puisoru M.(1),Fatu C.(1),Fatu A.(1),Fatu R.(1),Vascu B.(1),Fatu I.(2),

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Abstract:
This study aims to point out whether there are modifications in the pattern of vascularization in progression from simple to complex atypical endometrial hyperplasia and if the pathological aspects of angiogenesis could predict the progression to in situ adenocarcinoma.
The vascularization was quantitatively evaluated in 24 cases of endometrial hyperplasia using CD34 immunohistochemical staining of endothelial cells. The endothelial-to-stroma ratio was automatically calculated by a professional software Image ProPlus.
The results show an increase in endothelial-to-stroma ratio from simple to complex hyperplasia. The abundant vascular network in atypical lesions may indicate the progression to in situ adenocarcinoma.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:47

Titel:Molecular mediators and environmental modulators of pathogenesis in Huntington's disease

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Abstract:
Huntington's disease (HD) is a neurodegenerative disorder caused by a CAG repeat expansion encoding a polyglutamine tract in the huntingtin protein. HD involves selective degeneration of specific neurons, particularly in the striatum and cerebral cortex, leading to progressive cognitive, psychiatric and motor symptoms. We have characterised cognitive, affective and motor performance over time in the R6/1 transgenic mouse model of HD and correlated the behavioural findings with gene expression and cellular plasticity, following housing under different environmental conditions. We have then investigated specific aspects gene expression, neuronal morphology, synaptic plasticity and neurogenesis in selected brain regions of wild-type and HD mice, including the hippocampus, neocortex and striatum. Our findings demonstrate that environmental factors, in particular environmental enrichment, can dramatically modify the disease process and delay the onset and progression of motor and cognitive symptoms. We have also been able to model both the cognitive deficits and affective abnormalities, and correlate them with deficits of adult neurogenesis and cortical plasticity. Cognitive and affective deficits were found to occur prior to onset of motor symptoms in HD mice and may be mediated by 'pathological plasticity' at the cellular level. We have been investigating the mechanisms mediating these experience-dependent effects, and have identified spatiotemporally regulated molecular and cellular changes in response to environmental stimulation. Our findings indicate that the modulatory effects of environmental enrichment are mediated by experience-dependent changes in transcription of specific genes, synaptogenesis and adult neurogenesis, some of which may be mimicked by a newly proposed class of therapeutics ('enviromimetics').

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:48

Titel:The mice models for Alzheimer's disease

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Abstract:
The neuropathological diagnosis of Alzheimer's disease relies on the presence of two brain lesions, i.e. neurofibrillary tangles and senile plaques. Neurofibrillary tangles are composed of phosphorylated forms of the microtubule-associated protein tau and the main component of senile plaques is an extracellular amyloid deposit made of the Abeta amyloid peptide.
Most cases of Alzheimer's disease are sporadic, but pathogenic mutations of several genes (amyloid protein precursor, presenilines 1 and 2) have been identified in familial cases of Alzheimer's disease. Pathogenic mutations of the tau gene have also been identified in some familial forms of frontotemporal dementias. A leading hypothesis of Alzheimer's disease is the amyloid cascade that implies that Abeta peptide is the initial culprit leading to the formation of neurofibrillary tangles and/or neuronal death and synaptic loss. We will review here how transgenic models allow investigating this hypothesis. Transgenic mice overexpressing mutant amyloid protein precursor develop intra- and extracellular deposits of Abeta amyloid and co-expression of mutant presenilin 1 aggravates the amyloid pathology, but they do not develop neurofibrillary tangles. Transgenic mice overexpressing mutant tau develop authentic neurofibrillary tangles, but they do not develop amyloid deposits. These pathological phenotypes are associated in most cases with neuronal and synaptic loss. The full picture of pathological lesions can only be obtained in combined transgenic models. However, these models and others are helpful to decipher the cellular mechanisms leading to the development of these lesions and potential therapeutic approaches.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:49

Titel:The rat model for amyotrophic lateral sclerosis and its potential in development of stem cell therapy

Autoren: Mitrecic D.(1),Pochet R.(1),

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Abstract:
Amyotrophic lateral sclerosis (ALS) is a fatal and still incurable neurodegenerative disease characterized by fast deterioration of motor neurons. Death caused by paralysis occurs only 3 to 4 years after the first symptom is observed. Although majority of the cases are sporadic, familial subtype of ALS characterized by dominant inheritance attracted attention for mutation in superoxide dismutase 1 (SOD1) gene. In order to get insight in the pathological background of ALS, corresponding rat and mouse model encompassing various modifications of SOD1 gene are constructed. Moreover, availability of SOD1 animal model offers possibility to test various therapeutic approaches, including cell therapy and drug screening.

In order to test potential of neural stem cell therapy in the rat model of ALS, in vitro differentiation of neural stem cells obtained from embryo cortex of SOD1 mutant rat was analyzed. Observed facts included shift in expression of various differentiation markers and disturbed cell clustering. In order to test potential beneficial effect using blood delivery approach, 10 millions of wild type nestin/GFP positive cells were injected in the rat tail vein. Interestingly, after 3 days, injected cells were found in the cortex and hippocampus of treated animals.

Various ALS animal experimental models enable to test innovative therapeutic approaches for this fatal disease. Presence of injected neural stem cells in different regions of ALS affected rat brain after blood stream delivery represents important step further in cell transplantation therapy.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:51

Titel:The effect of NMDA glutamate receptor blockade in lurcher mutant mice during two periods of their ontogeny on hippocampal long term potentiation (LTP)

Autoren: Barcal J.(1),Cendelin J.(1),Korelusova I.(1),Tuma J.(1),Vozeh F.(1),

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Abstract:
To evaluate the effect of long-term NMDA glutamate receptor (NMDAR) blockade on the hippocampal LTP in an animal model of olivo-cerebellar degeneration - Lurcher mutant mice (LMM).
MK-801 (dizocilpine), noncompetitive NMDAR antagonist was administered in a dose of 0.2 mg/kg of body weight, daily during two periods of ontogeny: D5 – D26 and D91 – D111. The effect of influencing NMDAR on some behavioral characteristics was studied during 15 consecutive days using special methods. Then, LTP was done in LMM and also in their healthy littermates which served as controls (wild-type, WT).
LTP ability was described in animals of both types. Analysis of LTP in animals pretreated with MK-801 showed significant long-term supression of NMDAR activity, in both WT and LMM despite certain small differences. Statistically significant difference was also revealed in young control LMM (pretreated with saline) compared to control adult WT animals, when the level of LTP in Lurchers was paradoxically higher.
Our results show that cerebellar pathology and a physical activity can influence the “level” or “intensity” of NMDA receptor blockade and LTP in hippocampal region, too. It could be concluded that the results support the ideas about tight functional cooperation between the brain structures which are involved in mechanisms of learning and memory.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:52

Titel:Restoring appropriate cognitive function and plasticity in circuits associated with dysfunctions in coping with stress : a new approach to treat mood disorders

Autoren: Jay T.(1),

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Abstract:
Using different stress paradigms, we have developed an animal model based on measures of plasticity (LTP, dendritic arborization, memory function) on the key cognitive circuits connecting the hippocampus and prefrontal cortex. Exposure to acute and chronic stress causes a long-lasting alteration of long term potentiation (LTP) evoked in the prefrontal cortex by stimulation of the hippocampal outflow. Here we examine the effects of the structurally similar, but pharmacologically distinct, antidepressants, tianeptine and impramine, on stress-induced alterations in the phosphorylation state of receptors, signalling proteins in the prefrontal cortex.
Stress was evoked by placing rats on an elevated platform during 30 min. Tianeptine (10 mg/kg) and imipramine (10 mg/kg) were injected intraperitoneally just after the end of stress. Rats were killed 30 min later and compared to saline treated animals. Protein phosphorylation was determined by Western blot on snap-frozen frontal cortices. Immunoblotting was carried out with phosphorylation-state-specific antibodies against glutamate receptors, signalling proteins.
Acute treatment with the antidepressants tianeptine and imipramine reversed the stress-induced down-regulation of P-Ser217/221-MEK seen in frontal cortex 30 min after stress and caused a direct increase on P-MEK and P-MAPK. Tianeptine, but not imipramine, increased the phosphorylation of Ser831-GluR1.
The results demonstrate that stress-induced impairment of plasticity converge on a network of interactive effects on a putative BDNF/MEK/MAPK signaling cascade in the frontal cortex that is reversible by the antidepressants tianeptine and imipramine. Reversal of stress-induced impairment of frontal LTP by tianeptine may be associated with the phosphorylation of AMPA receptors.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:53

Titel:The superior colliculus as a model for plasticity and regeneration

Autoren: Martinez-Millán L.(1),Gerrikagoitia I.(1),Carril I.(1),

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Abstract:
The superior colliculus (SC) is located in the mesencephalon and structurally is made of alternate layers of neurons and fibres. Whereas superficial layers receive visual information, intermediate and deep layers are terminal fields for fibers coming from auditory, somatosensory, motor and limbic structures. In recent years our group was working in plastic changes that occur in collicular afferent systems after suppressing retinal afferents in neonatal stage. Two kinds of axonal sprouting were observed. The visual cortico-collicular connection reacts with a tangential expansion of its fibres ending in the stratum griseum superficiale. In contrast, auditory, limbic and somatosensory afferents that end in intermediate and deep collicular layers undergo a vertical ascending sprouting which results in an invasion of a visual territory like stratum griseum superfiale by stimuli of multimodal origin. When the retinal afferents are suppressed in adult animals, both tangential and ascendant sproutings are absent. In this model we tried to inhibit the expression of molecules like NOGOr that inhibits axonal sprouting. Treatment of visual cortex in adult animals after visual deafferentation was followed by a tangential sprouting showing a recovery of the growing capacity. This model offers the possibility to test an increase of sprouting capacity by visual and multimodal afferents after injection of candidate factors that have shown plastic or synaptogenetic effects in vitro.

Kategorie: Lecture

Rubrik: 14.Anatomical Record/Wiley symposium
Abstract Nr.:57

Titel:Epigenetic modifications of chromatin structure determine lung biology in health and disease

Autoren: Albertine K.(1), Metcalfe D.(1), Dong L.(1), Callaway C.(1), McKnight R.(1), Dahl M.(1), Moyer-Mileur L.(1), Yoder B.(1), Null D.(1), Lane R.(1)

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Abstract:
Chronic lung disease (CLD) of prematurity is characterized by alveolar simplification and altered gene expression. Long-term changes in phenotype and gene expression, in the absence of gene mutation, suggest that altered determinants of chromatin structure, such as histone acetylation, may be involved. Indeed, premature lambs that are ventilated for 3 days (3d) and treated daily with histone deacetylase inhibitors have more normal alveolar formation. In fact, alveolar formation is similar to that in preterm lambs managed by high-frequency nasal ventilation (HFNV), which is similar to nasal continuous positive airway pressure (nasal CPAP). Those findings suggest that ventilation mode affects histone acetylation in the lung, but whether the histone modifications persist is not known.
We hypothesized that 3-4 weeks of continuous ventilatory support with HFNV will result in normal alveolar formation that is associated with persistent histone hyperacetylation in the lung.
Preterm lambs (~132d gestation; term~150d), treated with antenatal steroids and postnatal surfactant, were managed by HFNV or MV for 3-4 weeks. Lung tissue was analyzed by morphometry/stereology for lung structure, RT-PCR for mRNA expression, immunoblot and immunohistochemistry for protein abundance and localization, respectively.
Normal alveolar formation characterized the lungs of preterm lambs managed by HFNV, whereas alveolar simplification characterized the lungs of other preterm lambs managed by MV. mRNA expression of enzymes that promote histone acetylation and protein abundance of acetylated histones were greater in the HFNV group compared to the MV group.
We conclude that ventilation mode affects the persistence of histone hyperacetylation in the lung of preterm lambs. We speculate that the environmental changes associated with preterm birth followed by prolonged MV results in dysregulated gene expression in the lung through an epigenetic mechanism. (HL62875, HL56401, HD41075, CHRC)

Kategorie: Lecture

Rubrik: 14.Anatomical Record/Wiley symposium
Abstract Nr.:58

Titel:Disturbance of distal airway morphogenesis and Clara cell function by interference with PPAR- and Wnt-signalling due to peroxisome deficiency.

Autoren: Karnati S.(1),Baumgart-Vogt E.(1),

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Abstract:
Only few knowledge is available on peroxisomes in Clara cells and on the role of peroxisomal metabolism during distal airway morphogenesis. In this study, we characterized the peroxisomal compartment and corresponding mRNAs in bronchioles of lungs of newborn and adult mice and man by morphological (IHC-IF-EM-ISH) and molecular biological methods (RT-PCR) and studied the pathological consequences of peroxisome deficiency in distal airway epithelia in PEX11beta knockout mice.
Our results show that Clara cells contain a high numerical abundance of peroxisomes and high levels of a variety of peroxisomal marker proteins (biogenesis proteins Pex13p and Pex14p, catalase and the beta-oxidation enzyme thiolase) in mouse and human lungs. In contrast, neighbouring ciliated cells of the bronchiolar epithelium exhibited only few peroxisomes with much lower content of the above mentioned proteins. ISH-experiments showed the strongest expression of PEX11beta-mRNA, encoding for a protein involved in peroxisome division, in the distal epithelia of bronchioles in newborn mouse lungs, in which Clara cells comprise 80% of the bronchiolar epithelial cells. PEX11beta knockout mice showed a significant retardation in the maturation of distal airways with altered Clara cells and significantly lower abundance of CC10. Pathological changes in Clara cells were noted in the content of ROS-metabolizing enzymes and of proteins involved in peroxisomal lipid degradation (ABCD3-ACOX1-upregulation). In addition, PEX11beta-deficiency decreased Wnt5a- and increased PPARdelta- and PPARgamma-mRNA expression levels, suggestive for a disturbance of these signal transduction pathways due to peroxisome deficiency, responsible for the interference in distal airway morphogenesis.

Kategorie: Lecture

Rubrik: 14.Anatomical Record/Wiley symposium
Abstract Nr.:59

Titel:Placodal and neural crest vagal C-fibers innervating murine airways: localization and phenotypic differences

Autoren: Nassenstein C.(1),Taylor-Clark T.(2),Myers A.(2),Ru F.(2),Bettner W.(2),Undem B.(2),

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Abstract:
The most common type of sensory nerve innervating the airways is the vagal C-fiber. Their cell bodies are located in the vagal nodose and jugular ganglia. The nodose neurons are derived from the placodes, and jugular neurons from the neural-crest. Little is known about the anatomy and phenotype of nodose and jugular vagal C-fibers in mice. By employing Wnt1Cre/R26R mice, that express beta-galactosidase only in neural-crest derived neurons, we found that the nodose ganglion structure per se actually comprises placodal neurons, but surprisingly also many neural-crest (jugular-like) neurons. The latter are situated in the rostral portion of the ganglion. In addition, some mice exhibited a distinct jugular ganglion structure that contained only neural-crest derived neurons. Neural-crest C-fibers did not respond to alpha,beta-methylene-ATP (an agonist for the heteromeric P2X2,3) whereas a distinct response was observed in virtually all placodal C-fibers. Using single-neuron-RT-PCR we found that most lung-labelled vagal C-fibers expressed P2X3, but only placodal C-fibers expressed P2X3 and P2X2. Only neural-crest C-fibers expressed preprotachykinin (PPT)-A. It has been suggested that the GDNF family receptors (GFRs) are involved in phenotype regulation of adult vagal sensory neurons. Both lung-innervating placodal and neural-crest C-fibers expressed RET, a co-receptor for GFRs, and most neurons also expressed GFRalpha1, but only the neural-crest C-fibers expressed GFRalpha3. In conclusion, murine neural-crest (jugular and rostral nodose) and placodal (nodose only) C-fibers can be reliably distinguished based on their responses to alpha,beta-methylene-ATP, and expression of P2X2, GFRalpha3 and PPT-A.

Kategorie: Lecture

Rubrik: 14.Anatomical Record/Wiley symposium
Abstract Nr.:60

Titel:Caveolin-1 is involved in tracheal but not bronchial cholinergic constriction in the mouse

Autoren: Krasteva G.(1),Schlenz H.(2),Wiegand S.(2),Kummer W.(2),

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Abstract:
Asthma is associated with hyperreactivity of the airway smooth muscle (ASM) causing extensive airway narrowing. In acetylcholine-induced airway constriction, muscarinic acetylcholine receptor subtypes 2 (M2R) and 3 (M3R) are involved. The contractile response to muscarine is decreased in urinary bladder of caveolin (Cav)-1-deficient mice (-/-), so that involvement of Cav in airway smooth muscle constriction can be hypothesized.
Videomicroscopy was performed to study bronchoconstriction in living precision cut lung slices (PCLS) from Cav-1-/- and wild-type (+/+) mice. Contractile response of the cervical trachea to muscarine and serotonin was studied in Cav-1-/-, M3R-/-, M2/3R-/- and the corresponding wild-type mice in organ bath experiments.
Bronchial luminal area decreased in PCLS from Cav-1-/- and Cav-1+/+ mice after stimulation muscarine concentration dependently (0.1 to 10 µM) without significant differences between both strains. In the trachea, the response to 1 µM muscarine was completely abolished in M2/3R-/- mice but was not statistically different from wild-type mice in M3R-/- mice. In cervical tracheal rings from Cav-1-/- mice, a reduction in contractile strength induced by 1 µM muscarine was detected compared to Cav-1+/+ mice, demonstrating an involvement of caveolin-1 in regulation of M2R-mediated contraction in murine trachea. Tracheal contractile response to 10 µM serotonin was increased in M3R-/- and M2/3R-/- mice compared to wild-type.
These results demonstrate a functional role of Cav-1 in the regulation of cholinergic tracheal but not in bronchial smooth muscle constriction. In addition, we clearly show the predominant role of the M2R in cervical tracheal muscle constriction.

Kategorie: Lecture

Rubrik: 14.Anatomical Record/Wiley symposium
Abstract Nr.:61

Titel:Sphingosine kinase 1 deficiency leads to increased remodelling and responsiveness of pulmonary vasculature in chronic airway inflammation

Autoren: Haberberger R.(1),Tabeling C.(2),König P.(3),Runciman S.(1),Gibbins I.(1),Witzenrath M.(4),

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Abstract:
The influence of sphingosine 1-phosphate(S1P)in vascular remodelling and reactivity in airway inflammation is unknown. We used mice, deficient in one of two S1P synthesizing sphingosine kinase (SphK) isoforms, SphK1, and the corresponding wild-type (wt) and models of ovalbumin induced airway inflammation to investigate the effects of SK1-deficiency on pulmonary vasculature.
QRT-PCR, histochemistry and immunohistochemistry in combination with stereological analysis were used to determine changes mRNA expression and airway structure. Changes in airway resistance and pulmonary arterial pressure were determined in response to methacholine or U46619.
Following 4 weeks of systemic ovalbumin sensitization and local airway challenge, airway responsiveness increased less in SphK1-/- as compared to WT mice, whereas pulmonary vascular responsiveness was greatly increased and did not differ between both strains. Acute lung inflammation led to an increase in eosinophils and mRNA expression for S1PP2 and S1P lyase in lungs of WT but not SphK1-/- mice.
Following repetitive allergen exposure for 8 weeks, airway responsiveness was not augmented in SphK1-/- or WT mice, but pulmonary vascular responsiveness was increased in both strains, with significantly higher vascular responsiveness in SphK1-/- as compared to WT mice. Increased vascular responsiveness was accompanied by remodelling of small and intra-acinar arteries with a significantly higher increase in wall thickness of SphK1-/- intra-acinar arteries.
The SphK/S1P pathway has been proposed as a target to design novel therapies to treat airway hyperresponsiveness. Our observations on SphK1-/- mice provide evidence that inhibiting SphK1 activity may be detrimental in allergic lung inflammation.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:63

Titel:Influences of the autonomic nervous system on the compensatory responses of the chick eye to defocus: single- and double-lesions studies of the pterygopalatine ganglion

Autoren: Schrödl F.(1),Brehmer A.(1),Neuhuber W.(1),Nickla D.(2),

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Abstract:
The role of the autonomic nervous system in eye growth regulation is unclear. We lesioned the pterygopalatine ganglion (PPG) alone, and in combination with the ciliary ganglion (CG) or the superior cervical ganglion (SCG), to study influences on the compensatory responses to defocus in chicks.
Preganglionic PPG lesions (PPGX), combined with CG/SCG transections (CGX/SCGX) were followed by visual manipulations in 19-28d-old birds:
PPGX: no manipulation; myopic defocus: +10D-lenses; hyperopic defocus: by lens removal/ -10D-lenses.
PPGX/SCGX: myopic defocus: +10D-lenses; hyperopic defocus: by lens removal.
PPGX/CGX: myopic defocus: +10D-lenses.
Eye dimensions were measured using A-scan-ultrasonography.
PPGX revealed no significant effects on ocular dimensions; eyes responded normally to all visual manipulations.
PPGX/SCGX inhibition of choroidal response to myopic defocus was significant (change over 3d: 274 vs. 376 mikrom; p<0.05); no effect on hyperopic defocus response.
PPGX/CGX revealed a significant lesion-induced increase in choroidal thickness over 5d (lesion vs. control: 83 vs. 1 mikrom; p<0.001) and a reduced choroidal response to myopic defocus (72 hrs: 66 vs. 319 mikrom; p<0.001). Despite the surgery-induced thickening, the response was still incomplete (149 vs. 319 mikrom; p<0.01). The difference in the axial growth response was not significant. Inhibition in anterior chamber growth was significant (lesion vs. fellow: 62 vs. 111 mikrom/72 hrs; p<0.001).
PPGX alone had little effect, while PPGX/CGX and PPGX/SCGX altered choroidal compensation to myopic defocus, with the ciliary input being more prominent. A role for the PPG in these responses however, cannot be excluded, because of the potential for as yet unknown interganglionic circuitries.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:64

Titel:Anti-inflammatory effect of retinoic acid on prostanoid metabolism in cortical astrocytes

Autoren: Johann S.(1),Kampmann E.(2),van Neerven S.(2),Mey J.(2),Beyer C.(1),

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Abstract:
Prostanoids participate in neuronal degeneration under toxic and pathological conditions. The cellular source of prostanoids during neurodegenerative diseases remains unclear. To identify astroglia as a likely source, the expression of prostanoid-metabolizing enzymes and their regulation by lipopolysaccharides (LPS) was analyzed in astrocyte primary cultures. The influence of retinoic acid (RA) known to be protective in the CNS was investigated after LPS-induced inflammation.
The expression of relevant synthesizing and catabolic enzymes for prostanoid production were analyzed with Affymetrix GeneChip Array and real-time RT-PCR in cultured astrocytes from neonatal mice For RA-mediated regulation, astrocytes were pretreated for 12h with all-trans RA and subsequently exposed to LPS for 12h. Prostaglandin E2 release into the cell culture supernatant was measured using an enzyme immunoassay. In addition, cyclooxygenase 2 (COX-2) protein was determined by immunoblotting of cell extracts.
Basal expression of relevant prostanoid metabolizing enzymes was found in astrocytes. LPS stimulated all enzymes required for PGE2 production and inhibited enzymes responsible for PGE2 degradation and synthesis of leukotrienes. RA significantly attenuated LPS-induced COX-2 expression, resulting in a significant net reduction of PGE2 production.
Our data suggest an active role for astroglia in brain PGE2 synthesis under pathological conditions. RA appears to be effective in suppressing PGE2 production. Future studies have to clarify the importance of RA as protective factor in suitable animal models of neurodegeneration and -inflammation.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:65

Titel:Gender-specific regulation of mitochondria morphology and function in astrocytes under toxic conditions

Autoren: Arnold S.(1),Singh S.(1),Misiak M.(1),Roemgens A.(1),Beyer C.(1),

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Abstract:
Astrocytes and sex steroids regulate neuronal growth, function, and survival by acting in concert. With respect to the role of mitochondrial fusion, fission, and respiratory chain function for cell survival, we have studied the effect of estrogen on these parameters. Male and female cells were analyzed separately to detect possible gender differences in their regulation.
Quantitative RT-PCR, viability analysis, measurements of ATP and ROS levels of primary astrocytes from female and male mouse brains were performed.
(1) Estrogen-treated female astrocytes demonstrated increased cell numbers accompanied by an up-regulation of fusion/fission gene transcription, thereby balancing pro- and anti-apoptotic processes. Male astrocytes revealed no changes in cell number. This might be the consequence of stimulated apoptosis in male astrocytes which is counterbalanced by increased proliferation by estrogen. Supportively, estrogen promoted fusion and fission gene transcription. (2) Application of mitochondrial toxins (3-nitropropionic acid) increased cytochrome c oxidase (COX) isoform IV-2 expression which is causally related to elevated intracellular ATP levels at the expense of increased mitochondrial ROS production and necrotic cell death. Estrogen suppressed the increase of COX IV-2 expression and its functional consequences, thus promoting cell survival.
Interactions of sex steroids with mitochondria may promote cell survival and represent an important mechanism for gender differences in cellular pathology in the CNS.

Kategorie: Lecture

Rubrik: 6.Neuroanatomy/Neurobiology
Abstract Nr.:66

Titel:Multimodal imaging of adherently cultured neural stem/progenitor cell implants in the brain of mice

Autoren: Reekmans K.(1),de Vocht N.(2),Tambuyzer B.(1),Bergwerf I.(1),Daans J.(1),Chatterjee S.(1),Jorens P.(1),Ysebaert D.(1),Van Marck E.(1),Van Der Linden A.(2),Berneman Z.(1),Ponsaerts P.(1),

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Abstract:
Stem cell transplantation is expected to become a promising therapeutic strategy for treatment of various traumatic and ischemic injuries to the central nervous system. However, for these pre-clinical animal studies, real-time visualization of stem cell transplants remained a challenging research topic. Therefore, in this study we aimed to investigate whether cellular implants of f-MPIO-labelled luciferase-expressing neural stem/progenitor cells (NSPC-LUC), can be monitored non-invasively by magnetic resonance imaging (MRI), and can be monitored simultaneously by bioluminescence imaging (BLI). For this, we first derived adherently growing NSPC cultures from ROSA26-L-S-L-Luciferase transgenic mice, which displayed a uniform morphology and expression profile. Activation of luciferase expression was induced by transfecting NSPC with messenger (m)RNA encoding the Cre recombinase protein, using an optimised mRNA lipofection protocol. In order to localise NSPC-LUC cell grafts pre-mortem by MRI and post-mortem by histology, we loaded our cultured NSPC-LUC with 0.96 μm green fluorescent micron-sized paramagnetic iron oxide (f-MPIO) particles. MRI can detect these f-MPIO particles upon implantation of f-MPIO-labelled NSPC-LUC in the CNS of immune-competent mice. In addition, cell viability was monitored simultaneously by pre-mortem BLI. Finally, histological analysis revealed an in vivo differentiation potential of implanted f-MPIO-labelled NSPC-LUC mainly into astrocytes, but not into neurons, at different time-points post-implantation. In summary, we here propose an experimental procedure to combine pre-mortem BLI and MRI with post-morten histological analysis in order to evaluate in vivo survival, localisation and differentiation of grafted NSPC in the CNS of immune-competent mice.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:67

Titel:Urinary proteomics via 2-d gel electrophoresis in human bladder cancer and chronic cystitis

Autoren: Turan Z.(1),Irmak S.(1),Ergün S.(1),

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Abstract:
2-dimensional gel electrophoresis (2-DE) is a powerful tool for analyzing proteins in complex mixtures such as in cell and tissue extracts or body fluids including urine and serum. Human urine plays a central role in clinical diagnostics of diseases like cancer or chronic cystitis.
The aim of the current study was to determine the protein pattern of urine samples of healthy donors, patients with bladder cancer of different stages and patients with chronic cystitis to identify new proteins which might be related to angiogenesis and growth of bladder cancer. At the beginning of the study we focused on optimization of preparation of urine samples to better preserve the urinary proteins prior to their use for 2-DE. We performed 2-DE on urine samples of patients with urinary bladder cancer (n=17) in different stages, patients with chronic cystitis (n=4) and healthy donors (n=8). Protein pattern of each group of urine samples were then compared with each other using PDQuest (Bio-Rad) and/or Delta2D (Decodon). Our results showed significant differences in protein pattern of urine samples of patients with bladder cancer and patients with chronic cystitis in comparison to that of healthy donors. In summary, our present data show that optimized 2-DE results in reproducible specific protein patterns, which seem to be useful to distinguish bladder cancer from healthy donors and those with cystitis. This study will probably allow to determine specifically the urine 2-DE-protein pattern for bladder cancer and cystitis, and to use this technique in bladder cancer diagnosis.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:68

Titel:Antirheumatic effects of sulforaphane: decrease of inflammation, proliferation and MMP activation

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Abstract:
The aim of the study was to evaluate the influence of the Isothiocyanate Sulforaphane (SFN) on Tumor necrosis factor-alpha (TNF alpha) induced inflammatory and destructive processes occurring in Rheumatoid arthritis (RA).
Cultured immortalised synovial fibroblasts were stimulated with TNF-alpha with or without SFN pre-treatment. The activity of the pro-inflammatory transcription factors NF-kappaB and AP 1 was investigated via Dual-Luciferase promoter-assay and cytokine secretion levels were detected using ELISA. Utilising CyQuant assay the synovial fibroblast proliferation was determined. Furthermore, the activation of Matrix Metalloproteinase 9 (MMP-9) was displayed by Zymography.
SFN treatment inhibits the TNF-alpha-induced NF-kappaB and AP 1 activation and expression of IL 1 and IL 6. In addition, SFN suppresses cell proliferation of synovial fibroblasts and TNF-alpha enhanced activation of MMP-9 in a dose-dependent manner.
Our results demonstrate that SFN may have, in addition to its antiphlogistic properties, an inhibitory effect on pannus formation and cartilage destruction in RA. All these properties make SFN a promising pharmaceutical lead for the development of a novel therapeutic agent for rheumatoid disorders.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:69

Titel:Involvement of phospholipase D 1 and 2 in the activity and signal transduction of formyl-peptide-receptors in the human colonic cell line HT29

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Abstract:
Epithelial cells of the alimentary tract play a central role in the mucosal host defence against pathogens and in the recognition of agonists that interact with mucosal surfaces. In particular, the formyl peptide receptor (FPR) family and their three human subtypes: FPR, formyl-peptide-receptor-like-1 (FPRL1) and FPRL2, are involved in the host defence against pathogens that mediate epithelial responses thus upregulating inflammation.
To elucidate the mechanisms by which formyl peptide receptors function, we examined the influence of phospholipase D (PLD) 1 and 2 on the activity and signal transduction of human enterocytes cell line HT29. PLD is a key enzyme involved in secretion, endocytosis and receptor signalling. We inhibited PLD1 and 2 by small interference RNA (siRNA) and determined the activity of formyl peptide receptors using western blotting and cAMP level measurements. We then analyzed the distribution of formyl peptide receptors FPR, FPRL1 and FPRL2 compared to a control.
In this study, we demonstrated that the depletion of PLD1 and 2 resulted in a marked reduction of formyl peptide receptor activity due to inhibited extracellular-signal regulated kinases 1/2 (ERK1/2), phosphorylation and cAMP level reduction. In addition, we observed an intracellular accumulation of FPR, FPRL1 and FPRL2 as a result of receptor recycling inhibition using fluorescence microscopy. The constitutive internalization rate was remained unaffected.
Our results support the importance of PLD1 and 2 in formyl peptide receptor function and the role of endocytosis, receptor recycling and reactivation for receptor activity.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:70

Titel:The role of platelet rich plasma (PRP) in fracture healing

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Abstract:
Healing of open fractures are often impaired due to bacterial infection and the defect dimension. Aim of the study was to elucidate the beneficial influence of Platelet Rich Plasma (PRP) and Platelate Rich on Growth Factors (PRGF) on proliferation, migration and cytokine expression of osteoblasts.
Platelets and subsequently PRP were obtained from healthy human donors. The release of antimicrobial peptides (AMPs) and the Bone Morphogenetic Protein (BMP4) from platelets were investigated by Western Blot and ELISA. For this study osteoblasts were cultured and incubated with PRGF. Cell proliferation was measured using CyQUANT ® assay.
Scratch test was performed using a microliter pipette tip on monolayer of human osteoblasts (NIKON). The radial disk diffusion test was carried out to evaluate the antimicrobial activity of PRP.
In this study we could demonstrate the expression of the antimicrobial peptides human beta defensin- 2 and -3 (HBD-2 and hBD-3) in PRP. We could further demonstrate that PRP leads to a release of osteoinductive BMP-4. Further we could show with scratch test that PRGF induces wound healing and cell migration.
The use of PRP in fracture healing could reduce the risk of infection due to the existence of hBD-2 and -3. An increase of cell proliferation, cell migration and the release of osteoinductive proteins may reduce the duration of fracture healing. The therapy using autologous PRP or PRGF in order to increase fracture healing and prevention of bone infection seems to be a proper addition to conventional therapy.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:71

Titel:Cross-talk between natriuretic peptide receptors and its impact on vasorelaxation

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Abstract:
There are different mechanisms to regulate biological activity of natriuretic peptides: first by modulating activity of their cognate receptors guanylyl cyclase (GC)-A (GC-A) and -B (GC-B), secondly via involvement of the natriuretic peptide clearance receptor and finally by membrane-bound proteases, reducing extracellular hormone availability. GC activity is regulated by changes in the degree of receptor phosphorylation, while dephosphorylation reduces receptor responsiveness to its ligand. Previous studies revealed homologous (ANP/GC-A-dependent) and heterologous (ANP/GC-A-independent) desensitization of the ANP receptor GC-A in MA-10 Leydig cells, which do not express the CNP receptor GC-B.
To investigate whether GC-A activity is affected by co-expression of GC-B in the same cell, alphaT3 and vascular smooth muscle cells, which were found to express both enzymes, were used. GC assays indicated homologous desensitization of GC-A (mediated by cGMP-dependent protein kinase I), but not of GC-B. ANP/GC-A had no effect on GC-B activity. Surprisingly, however, CNP/GC-B augmented GC-A activity. The cAMP-dependent protein kinase was shown to be involved in this CNP/GC-B-mediated GC-A sensitization. Isometric tension recordings confirmed this data. CNP/GC-B enhanced the vasorelaxing effect of ANP and relieved ANP-dependent GC-A desensitization.
Our results revealed a novel signaling pathway, by which CNP can increase hormone-sensitivity of GC-A. This mechanism is present and active in the vasculature to regulate the vasodilatory potency of ANP. Desensitization of GC-A, expected to take place under conditions of elevated ANP plasma levels, can be relieved by CNP/GC-B signaling. Data suggests a considerable therapeutic potential of GC-B agonists.

Kategorie: Lecture

Rubrik: 8.Cell Biology
Abstract Nr.:72

Titel: Curcumin promotes adequate microenvironment for MSCs differentiation to chondrocytes during osteoarthritis

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Abstract:
Traumata of the articular cartilage lead to degenerative changes of the cartilage tissue often resulting in osteoarthritis (OA). Although recent studies have shown that also in articular cartilage tissue mesenchymal stem cells (MSCs) are resident, osteoarthritic cartilage has poor self-regeneration capacity and OA poses a huge challenge for modern medicine. The high content of cytokines (TNF-α, IL-1β) present in OA are a known promoter of OA and may prevent the adequate chondrogenic differentiation of these cartilage resident MSCs. The plant extract Curcumin, derived from dried rhizomes of Curcuma longa, has been shown to inhibit inflammation in chondrocytes through inhibiting the IL-1β-induced activation of NF-κB and Caspase-3 as well as PARP cleavage. The aim of the presented study was therefore to evaluate whether Curcumin can promote adequate chondrogenic differentiation conditions for MSCs in an OA co-culture model of MSCs and primary chondrocytes (PCh), by inhibiting cytokine action.Bone marrow MSCs were cultured in a ratio of 1:1 in high density culture with primary isolated chondrocytes with curcumin and IL-1β for various time points and combinations. High density cultures of pure MSCs and pure chondrocytes were used as controls. The high density cultures were evaluated with light- and electron-microscopy and western blotting. Light- and Electron-microscopy demonstrated that sole treatment of MSCs or PCh with IL-1β resulted in apoptosis and necrosis of the MSCs and PCh without formation of cartilage specific extracellular matrix (ECM). Sole treatment of MSCs with Curcumin did not enhance MSCs chondrogenic differentiation. In the co-cultures treatment with IL-1β alone lead to apoptosis and necrosis. Contrary to this, co-cultures treated with normal cell culture medium developed large and round cells surrounded by a well developed ECM, typical for cartilage formation. Interestingly, co-cultures treated with IL-1β and Curcumin, either simultaneously for 14 days or with a 4 hour pre-treatment of Curcumin followed by 14 days of Interleukin-1β treatment, developed into well organised, cartilage like structures surrounded by a perichondrium like structure. Western blot analysis demonstrated in these co-cultures high amounts of collagen type II, cartilage specific proteoglycans, β1-Integrins, activation of the adaptor protein Shc, of ERK1/2 and of the chondrogenic transcription factor Sox9. Apoptosis (Caspase-3) and inflammation (Cox-2) markers were downregulated. We found that the chondrocytes provide an inductive differentiation signal to the MSCs activating the appropriate chondrogenic signaling pathways. IL-1β interferes in this interaction, inhibting MSCs activation and chondrogenic differentiation. The plant extract Curcumin, inhibits the signalling activity of Interleukin-1β thereby enhancing the formation of an adequate microenvironement for the differentiation of MSCs through close contact with the chondrocytes. These results open up new exciting possibilities for the clinical use of Curcumin for prophylaxis and for the treatment of OA.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:73

Titel:Multiple variations of arteries in the lower leg should be considered for pedal bypasses in case of the diabetic foot syndrome

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Abstract:
The diabetic foot syndrome is a dreadful complication of diabetes. To preserve the lower limb, crural and pedal bypasses are performed between the main arteries. We studied the variations of arteries in relationship to surgical intervention and outcome.
The popliteal, tibial and fibular arteries and the foot arteries of six alcohol-fixed cadavers (two men, four women; 82 to 94 years of age) were dissected after application of a special plastic and marked with colours. Additionally, we examined the blood vessels of lower legs from Thiel-fixed cadavers (two women, three men; 78 to 91 years of age). The fixation is recommended for the maintenance of in situ conditions and allows digital subtraction angiography.
The three-dimensional reconstruction of digital substraction angiography showed high variations of the main arteries and their anastomosis.
The following variations occurred: trifurcation, anterior tibial artery originating from the fibular artery, dominant fibular artery, plantar arch running through the second interosseus space, dominant deep plantar artery, deep branch of the medial plantar artery, prominent arcuate artery. The arteries for the plantar arch varied manifold and supplied most of the foot arteries. The medial plantar artery always appeared to a minor degree.
Surgeons should examine the prominent arteries and dorso-plantar anastomosis with the plantar arch for successful crural and pedal bypasses in diabetic patients with respect to individual variations.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:74

Titel:Anatomo-clinical correlations in orbital varices

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Abstract:
The study reveals the anatomo-clinical features of the orbital varice, venous anomalies which can be divided into two types: congenital, because of a mural weakness of the orbital veins or secondary to an intraorbital or intracranial arteriovenous communication through the superior orbital fissure. Two cases are presented, one for each type. They were investigated by using clinical methods, completed by ultrasonography and magnetic resonance imaging techniques.
The clinical assessment revealed the presence of intermittent proptosis, episcleral venous congestion and the secondary elevated intraocular pressure. These were accompanied by venous anomalies at the lids, conjunctiva or inferior limbs. Ultrasonography associated with color Doppler echography showed the morphology and the characteristics of the blood flow at the level of the orbital vessels. Magnetic resonance imaging completed the morphological data and revealed the presence of the intracranial vascular anomalies.
Orbital varices are manifested through multiple neuroophthalmological signs which have to be understood taking into account the basis of the anatomical correlations between the complex orbital structures. Imaging methods were helpful to determine the correct anatomo-clinical diagnosis and to take the adequate therapeutical decision.

Key words: orbital varices, anatomo-clinical features.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:75

Titel:Features of osteology in stylopodium and zeugopodium of *Didelphis marsupialis*

Autoren: Narain F.(1),van Zwieten K.(2),Gervois P.(2),Lippens P.(2),Op 't Eijnde B.(2),Vandersteen M.(2),Colla P.(2),Palmers Y.(2),Mewis A.(3),Lamur K.(1),

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Abstract:
Research in experimental (EAE) animals makes use of foot and ankle extensor muscles tibialis anterior and extensor digitorum longus to evaluate exercise therapy in chronic neuropathies(1). Because locomotion in EAE rats and other rodents shows less similarity to human gait than locomotion in non-human primates and predecessors like opossum rats, it may be useful to take into account the functional morphology of opossums as well (2).
In spite of the abundance of functional and morphological data on opossum hindlimb osteology, some osteological characters of the Didelphis marsupialis hindlimb remained hitherto unsatisfactory described (3). This is especially so, if observed from standard anatomical views.
Standard anatomical pictures of bony specimens of Didelphis marsupialis hindlimb stylopodium and zeugopodium were obtained by means of macrophotography. Line drawings of these photographs were then used to describe in detail functionally relevant features of the bones. Tuberositas tibiae, collum fibulae and spatium interosseum cruris appear to be reliable landmarks to describe non-sagittal plane movements of the opossum hindlimb in stance and sway. Recognition of such osteological features in both rodent and primate locomotion is therefore suggested.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:76

Titel:Functional organization of the foramen lacerum

Autoren: Antohe I.(1),

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Abstract:
Our study proposes to precise the mode of foramen lacerum formation, correlated with superior orifice of carotic canal and sphenopetroclival structures.
The anatomical material studied consists of 87 dried skull bases (174 halves) and 100 skull base CT examination from nonneurological patients. The skulls were observed by means of Zeiss surgical microscope and the images were recorded on Sony video line or on Sony 717 digital camera.
Our study allowed us to demonstrate the mode of superior carotic orifice formation and the triangular shape of “normal” foramen lacerum. In the most part of cases we have found a larger foramen with anterior sphenoidal and posterior petrosal contours with spinous prominences that give attachment to the petrosphenoidal membrane and for various sutures for which we have propose an original nomenclature.
Conclusions. In our opinion, the foramen lacerum, covered by the petrosphenoidal membrane might be regarded as a basal fontanella that assures the transversal growth of skull base and also as a portvessel and portnerve structure for various preganglionic pertosal branches.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:77

Titel:The ligaments of the sacro-iliac joint

Autoren: Steinke H.(1),Hammer N.(1),Böhme J.(2),Stadler J.(3),Slowik V.(4),Josten C.(2),Spanel-Borowski K.(1),

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Abstract:
The ligaments of the sacro-iliac joint (SIJ) were investigated morphologically and morphometrically. Measures and positional relationships of the anterior (ASL), the interosseous (ISL) and the posterior sacroiliac ligament (PSL) were recorded and different methods of ligament visualization were compared in an anatomical study. Little is known about the SIJ ligaments, especially about the ISL. Pelvic computer simulations neglect these ligaments. The poor clinical outcome of patients who underwent operations on the SIJ supports the need of further investigations in the field of the SIJ ligaments. CT images and 7-tesla MR images of the SIJ of one male and one female specimen have been obtained by corresponding thin slice plastination. Frozen sections of the SIJ of 32 specimens (13 male, 19 female) were created to gather information of the SIJ ligaments. By means of the MR images and the plastinates, volumes of the SIJ ligaments could be rendered digitally. Geometric figures were then compiled for the SIJ ligaments. They allowed precise measurements of the ASL, the ISL and the PSL, including positional relationships. Statistically, the ASL and the PSL were larger in males, while the ISL was larger in females. The ISL volumes and origin surfaces were found to be the largest, while the ASL and the PSL measures were similar. The combined use of high-resolution MRI and thin slice plastination allows precise reconstructions of the SIJ ligaments based on substantive data. For the first time, the structures could be visualized in situ and described using high resolution techniques.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:78

Titel:A different point of view on pelvic floor function: the levator hiatus.

Autoren: Wallner C.(1),Dabhoiwala N.(2),DeRuiter M.(3),Lamers W.(1),

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Abstract:
The anatomy of the pelvic floor is complex and difficult to dissect or visualize. Therefore controversies on its architecture and function prevail. Here, we therefore opt to present the anatomy of the pelvic floor from a different point of view, i.e., from the point of the levator hiatus, because the pelvic organs pass through the puborectalis muscular sling of the levator ani muscle at this level. For this reason, the levator hiatus is crucial for proper pelvic-organ support and pelvic floor function.
We investigated (immuno)histochemically stained serial sections of the pelvic floor of foetuses and adults and prepared 3D-reconstructions.
The pelvic floor muscles can be divided into a superficial layer (bulbospongiosus, ischiocavernosus, external anal sphincter muscles) and a deep layer (levator ani and external urethral sphincter muscles). In the female (but not in the male), the external urethral sphincter is attached to the puborectalis muscle. Furthermore, a well-developed smooth-muscle layer anchors the pelvic organs to the medial border of the puborectalis muscle. The levator hiatus itself is guarded by the superficial muscle layer of the pelvic floor.
Since the puborectalis component of the levator ani muscle, functions as a site of attachment for the external urethral sphincter and the smooth-muscle which anchors the pelvic organs to the pelvic floor, the puborectalis needs to be physically and functionally intact for proper function of the pelvic floor. The superficial layer of pelvic floor muscles is an often neglected but important part of the pelvic-organ support system.

Kategorie: Lecture

Rubrik: 5.Experimental Morphology
Abstract Nr.:79

Titel:Upright trunk posture and bipedalism – adaptations in the lumbar perivertebral musculature

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Abstract:
Despite upright trunk posture and different contribution of trunk movements to body propulsion during bipedalism back muscle topography and activation patterns during walking are similar in humans compared to quadrupedal mammals. Additionally, conclusions drawn from muscle topography and EMG data concerning the function of these muscles are conflicting. To get further implications on the function of the muscles associated with the lumbar spine, their anatomical cross sectional areas as well as the distribution pattern of the two main muscle fibre types were investigated. The results were compared to data of quadrupedal mammals.
The determination of the anatomical cross sectional areas was based on CT scans and the images provided by the Visible Human Project®. The proportion of type I and type II fibres was determined over the whole muscular cross section along the lumbar spine of three donated male bodies. For this, the fibres were marked on consecutive serial sections of the perivertebral muscles using immune-histochemistry.
The more or less equal distribution of muscle fibres of both types over the muscles' cross sections is consistent with the EMG results and contradicts a simple stabiliser/mobiliser-scheme suggested considering topography. Even taking into account the age of the donated bodies and human body mass, our results point to an increased percentage of type I fibres in adaptation to upright trunk posture and bipedalism. The anatomical cross sectional areas of the perivertebral muscles also showed some differences suggesting different roles of the muscles in humans and other mammals.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:82

Titel:An experimental model for cognitive disorders

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Abstract:
To develop behavioral and electrophysiological recording techniques susceptible of being applied to wild-type and genetically manipulated animals simulating neurological and cognitive diseases.
Wild-type and genetically manipulated animals are prepared for the classical conditioning of eyelid responses or for instrumental learning using different training paradigms. Animal's phenotype is also determined using laboratory standard procedures (actimeter, passive avoidance, object recognition, startle response and pre-pulse inhibition, Rota-rod, and related techniques). Electrophysiological properties of precise synaptic relay sites (hippocampal and cerebellar circuits) can also be determined in alert behaving animals.
The proposed model allows the study of the functional properties of selected synaptic sites, including input/output curves and paired-pulse interactions. It is also possible evoking long-term potentiation (LTP9 or depression (LTD) in behaving animals. LTP has been followed in the same group of animals > 30 days. Mainly, it is possible to determine activity-dependent synaptic changes in strength across both classical and instrumental conditioning in cerebral cortical structures in both wild-type and transgenic and other types of genetically manipulated mice.
The proposed model is susceptible of being used in any type of adult mice provide they present a body weight > 20 g and that they are able of surviving by themselves. Thus, this model could be of a great help for determining phenotypic and cerebral electrophysiological properties in mice emulating precise brain diseases.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:83

Titel:In vivo global neurodegenerescence follow up using bioluminescence imagery in drosophila

Autoren: Martin J.(1),Murmu M.(1),

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Abstract:
Functional imaging studies based either on fluorescent Ca2+ sensitive dye or genetically encoded proteins have been performed to study the neural code underlying various neurophysiological functions. However, because these probes require light excitation, reducing the signal-to-noise ratio as a result of autofluorescence and photobleaching, thus, in-vivo imaging of the whole brain and particularly on deeply located structures has remained difficult. Recently, a new genetically encoded Ca2+ sensitive bioluminescent reporter, GFP-aequorin has been developed, allowing long term imaging, in continuous, to functional map neuronal circuits. We have developed GFP-aequorin transgenic flies together with the P[GAL4] system, for targeting GFP-aequorin to different brain structures, to functionally study, in-vivo, neuronal activity (Martin et al., PLoS-ONE, 2007). First, we show that we could visualise the neuronal activity in various structures of the brain, as the Mushroom-Bodies, the main structures implicated in olfactory learning and memory, or in the central complex, a structure controlling the locomotor activity. Moreover, we also show that ubiquitously expressing GFP-aequorin in all the neurons of the brain allows following the general activity of the whole brain, as an ensemble, over long time recording period, as hours. Similarly, expressing GFP-aequorin specifically in glial cells allows functional visualisation of glial cells activity. Therefore, this new approach could now be use to undertake, in-vivo, anatomo-functional mapping study of the Drosophila brain, in different experimental or behavioural conditions, as well as in different mutants and/or pathological context, as the Drosophila model/system of neurodegenerative diseases.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:84

Titel:Ischemic model of Alzheimer's disease

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Abstract:
We will critically review inconsistencies between the predictions of the "amyloid hypothesis" of Alzheimer's disease (AD) and the published data. At least one third of AD cases exhibit ischemic changes. In short, micro- and macroinfarctions and ischemic white matter changes are evident in brains. The presence of ischemic pathology seems usually ignored and regarded by researchers as insignificant in AD. Interestingly, that Alzheimer at 1907 in his own report described changes in the brain of first patient that besides "storage of peculiar material in the cortex, one sees endothelial proliferation and also occasionally neovascularisation". Endothelial proliferation and angiogenesis and moderate arteriosclerosis in the brain arteries of first case provide evidence that ischemic pathology was evident in the original case of AD. These rise the question what was the first ischemia as trigger of AD or neurodegeneration of Alzheimer's type itself? New findings propose an early and significant role for ischemia contributing to the neurodegeneration in AD. In this review we will show that brain ischemia produce neurochemical and neuropathological changes that simulate stages of AD process. Presented data suggest that ischemic mechanisms of neuronal death with amyloid peptide from circulatory network modulate neuropathology of cerebral ischemia injury via molecular events in common with Alzheimer-type neuropathology. Taken all together, evidence presented in this review suggests a scheme for Alzheimer's pathogenesis with ischemia playing a crucial role in influencing neuronal death and ischemic blood-brain barrier linking to amyloid peptide deposition in specific areas of brain.

Kategorie: Lecture

Rubrik: 7.Neuroimmunology
Abstract Nr.:86

Titel:Studies on an in vivo model of impaired interleukin-1 signalling

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Abstract:
Interleukin-1 (IL-1) is one of the most important proinflammatory cytokines in the immune response to infection, and is also implicated in neuroinflammation associated with several neurodegenerative disorders, such as cerebral ischaemia and Alzheimer's disease. IL-1 is also involved in many physiological processes, including brain development and the modulation of learning and memory processes. The previously developed (Lundqvist et al, 1999, Am J Physiol 276:R644-R651) mouse strain overexpressing human soluble IL-1 receptor antagonist (TghsIL-1ra) provides a useful tool in studies of IL-1 receptor (R)-mediated activity in the brain, since transgenic expression is under control of the GFAP-promoter.
Studies on effects of blocking IL-1R-mediated activity on neurogenesis in young and ageing mice, and upon kainic acid-induced excitotoxicity show a blunted neurogenesis response in the TghsIL-1ra mice. Similarly, the reaction of astrocytes and microglia to either acute or chronic inflammation is dramatically reduced.
Prenatally, IL-1 has been shown to stimulate the precursor cells in the mesencephalon to differentiate into dopamine-producing neurons, while in adults it causes degeneration of dopamine-neurons. Behavioural studies of the TghsIL-1ra mice indicate an anxiolytic effect and mild ataxia, suggesting influence on the dopaminergic system.
Neuronal IL-1 expression is enhanced following LTP, but exogenously added IL-1, or blocking IL-1 receptors inhibits the consolidation of memory. Studies on the learning ability in the TghsIL-1ra mice support the role of IL-1R-mediated signalling in long-term memory. Analysing the expression of activity-regulated cytoskeleton-associated protein (Arc) provide evidence for impaired synaptic strengthening underlying the learning defects.

Kategorie: Lecture

Rubrik: 4.Gross Anatomy/Clinical Anatomy
Abstract Nr.:87

Titel:The sacrotuberous and the sacrospinous ligament - a virtual reconstruction

Autoren: Hammer N.(1),Steinke H.(1),Slowik V.(2),Hülse R.(3),Stadler J.(4),Böhme J.(3),Spanel-Borowski K.(1),

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Abstract:
Little is known about morphometric and physical properties of the sacrotuberous ligament (ST) and the sacrospinous ligament (SS). The influence of ligaments on pelvic stability and the extent of reconstruction in case of instability are controversially discussed. The ST and the SS of 55 human subjects fixed in alcohol solution and of four fresh cadavers were measured. Both ligaments were defined as geometric figures. The ST was a contorted bifrustum, while the SS was a contorted frustum, both with elliptic planes. In all cases investigated, the ST and the SS fibers were twisted. For men, the ST and the SS had a mean length of 64 mm and 38 mm. For women, lengths of 70 mm and 46 mm were measured in the ST and the SS. The ST length, height and cross-sectional area showed gender-specific differences at statistically significant level. The ST and the SS volumes correlated closely, regardless of gender or side. Measurements of fresh ligaments of four unfixed cadavers showed similar results. The data obtained were then used to generate computer-based three-dimensional models of both ligaments, using Catia® as a software. Finally, the Young's modulus (E) was tested as a physical parameter in the ST and the SS of another three unfixed cadavers. The ST had a mean E value of 33 N/mm2, while the SS had an average E value of 19 N/mm2. Conclusively, the virtually generated ST and SS are adequate models to be included in pelvic fracture simulation, using the finite element method.

Kategorie: Lecture

Rubrik: 13. COST B30
Abstract Nr.:88

Titel: Neurodegeneration in peroxisomal diseases.

Autoren: Eveline Baumgart-Vogt (1),

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Abstract:
Peroxisomes are ubiquitous cell organelles, intimately involved in the metabolism of ROS and lipid derivatives. Peroxisomes harbour enzymes for synthesis of glycero- and ether lipids as well as cholesterol, which are incorporated into plasma membranes and especially also in myelin sheaths of the central nervous system. In addition, peroxisomal enzymes metabolize a variety of bioactive and signalling lipid derivatives, which serve as ligands for distinct nuclear receptors. If accumulated, continuous activation of these transcription factors may lead to severe disturbances of cellular homeostasis - in worst case the induction of cell death. The vital importance of peroxisomes for human health is stressed by the devastating diseases, which result from defective peroxisomal biogenesis or even from single enzyme deficiencies in peroxisomal lipid metabolism. Many of these patients show severe central nervous system defects, such as migration defects in the neocortex and the cerebellum, hypo- and demyelination of neurons, neurodegeneration in various brain and spinal cord areas, as well as reactive astrocytosis in affected areas. With the help of several different knockout mouse models, deleted in distinct peroxisomal biogenesis genes (PEX-genes), several aspects of the molecular pathogenesis of neurodegeneration in peroxisomal disorders have been studied in recent years. Current concepts for the molecular pathogenesis of neurodegeneration in peroxisomal disorders will be reviewed and original data supporting these theories will be presented, including severe alterations of ROS metabolism in neurons, leading to oxidative stress, induction of ER-stress and severe interference with nuclear receptor pathways and lipid signalling in the CNS.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:89

Titel:Neural stem cell grafts in a MS animal model

Autoren: Copray S.(1),

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Abstract:
A major issue in the potential application of neural stem cell (NSC)-based cell replacement therapy for demyelinating diseases is the question regarding the survival, functional behaviour and stability of implanted NSC-derived OPCs over an extended period. To address this issue, we have employed Bioluminescence Imaging (BLI) as a non-invasive longitudinal in-vivo monitoring technique and followed the fate of NSCs, isolated from luciferase-GFP-actin transgenic mice, after stereotactic implantation in the demyelinated corpus callosum of cuprizone-fed mice. We compared normal NSCs with NSCs that were primed to become OPCs by the induction of Olig2 overexpression (Olig2-NSCs) (Copray et al., 2006). BLI,validated by immunohistochemistry revealed that, after a steep cell loss after implantation during the first 3 weeks, approximately 10% of the Olig2-NSCs stably survived for two months after implantation, in contrast to <1% of the normal NSCs. Immunohistochemistry at light and electronmicroscopic level, revealed that the surviving Olig2-NSCs, in majority, had differentiated into an oligodendrocytic cell lineage and contributed to remyelination of axons in the corpus callosum. The number of axons remyelinated by the implanted cells, however, was a small fraction of the total number of axons remyelinated by endogenous oligodendrocytes. Apparently, most of the implanted NSCs do not survive the transition into an inappropriate nonneurogenic niche, compressed by surrounding host tissue, in hostile, inflammatory conditions created by activated microglia. Only the ones that manage to differentiate rapidly into a mature neural cell type and become functionally integrated, survive.

Kategorie: Lecture

Rubrik: 7.Neuroimmunology
Abstract Nr.:90

Titel:Allogeneic stromal cell implantation in brain tissue of immune-competent mice leads to robust microglial activation and subsequent graft elimination.

Autoren: Tambuyzer B.(1),Bergwerf I.(1),Reekmans K.(2),De Vocht N.(3),Daans J.(1),Ysebaert D.(4),Chatterjee S.(5),Van Marck E.(5),Berneman Z.(2),Ponsaerts P.(2),

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Abstract:
We aimed to investigate the immunological aspects of allogeneic bone marrow derived stromal cell (BM-SC) transplantation in the central nervous system (CNS) of immune-competent mice. Microglia (FVB-derived) and autologous (FVB) or allogeneic (C57BL/6-derived) BM-SC were co-cultivated and screened for TNF-alpha and NO production. BM-SC were injected intra-cranially followed by histological analysis. The immune responses raised against the allografts in vivo, were analysed using IFN-gamma ELISPOT.
Upon co-cultivation microglia nor BM-SC produced significant amounts of TNF-alpha or NO. Moreover, if these co-cultures were further stimulated with the IFN-gamma/LPS cocktail, no reduction or increase of TNF-alpha production was detected, while NO secretion was only slightly increased. After implantation of the allogeneic BM-SC in the brain, we observed vigorous microglial activation up till 4 weeks post-implantation, demonstrated by CD11b staining, whereas no other inflammatory cells could be detected at the site of transplantation. Simultaneously the BM-SC marker Sca-1, in the early post-transplantation phase used to detect the graft, was absent at 4 weeks post-implantation indicating graft elimination. Using CD3 staining, we also did not detect significant T-cell infiltration. The latter histological finding was further corroborated by the absence of systemic immune responses against intra-cranial implants. In contrast, immunological rejection of intra-muscular injected allogeneic BM-SC was detectable by IFN-gamma ELISPOT with splenocytes from cell-implanted mice.
(1) Microglia are not activated or inhibited by allogeneic BM-SC in vitro. (2) Rejection of allogeneic BM-SC implanted in the CNS of immune-competent mice is mainly mediated by activated microglia without overt T-cell involvement.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:91

Titel:Effects of either preoperative or postoperative or pre- and postoperative treadmill training on the recovery of motor function after immediate repair of the sciatic nerve in rats

Autoren: Barham M.(1),Andermahr J.(2),Majczynski H.(3),Slawinska U.(3),Stützer H.(4),Neiss W.(1),

Adressen:(1)Institut I für Anatomie|Universität zu Köln|Köln|Germany; (2)Klinik und Poliklinik für Unfall-, Hand- und Wiederherstellungschirurgie|Klinikum der Universität zu Köln|Köln|Germany; (3)|Nencki Institute of Experimental Biology|Warszawa|Poland; (4)Institut für Medizinische Statistik, Informatik und Epidemiologie|Klinikum der Universität zu Köln|Köln|Germany; email:neiss.anatomie@uni-koeln.de

Abstract:
Improvement of gait during sciatic nerve regeneration by treadmill training.
5 mm of the right sciatic nerve were excised and reconstructed with an allograft in Lewis rats that were additionally treated with A) preoperative running only, B) both pre- and postoperative running, C) postoperative running only, D) no treadmill-enforced movement. Reinnervation was studied with electromyography, walking track analysis and retrograde labeling of motoneurons. Animals were trained (9x250 m/week; max. speed 50 cm/s) for 12 weeks before and/or after nerve surgery. Walking tracks and the evoked compound muscle action potential (CMAP) of the soleus muscle were recorded before and 13 weeks after nerve transplant. Then motoneurons of the soleus and the fibular nerve were labeled with Fast-Blue or DiI, respectively.
In normal rats the Sciatic Functional Index was around 0, after sciatic nerve transection this value dropped to -46 and was further reduced to about -51 after transplant in all groups A-D. The amplitude of the CMAP was 16.5mV in normal rats, but reduced to 11.9mV (group A), 6.3mV (B), 8.1mV (C) and 6.5mV (D) after surgery. The latency of muscle contraction was 2.1ms in normal rats, but elevated to 3.1ms (A), 3.3ms (B), 3.2ms (C) and 3.1ms (D) after surgery. 549±83 motoneurons were labeled with DiI or Fast-Blue in normal rats, but only 505±202 (A), 466±108 (B), 436±78 (C) and 465±86 (D) regenerated motoneurons after nerve repair.
Only treadmill walking of rats before nerve damage improved recovery of function. – Supported by COST B30 NEREPLAS.

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:92

Titel:Reductions in KCC2 expression and changes in its intracellular distribution pattern in hypoglossal motor neurons precede tongue motility deficits in the SOD1-G93a mouse model of ALS

Autoren: Schütz B.(1),Fuchs A.(2),Schneider H.(3),Weihe E.(1),Roeper J.(2),

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Abstract:
In amyotrophic lateral sclerosis (ALS) some cranial somatomotor neuron nuclei degenerate, while others survive. Since excitotoxicity is considered to play a causal role in the pathogenesis of ALS we speculated that a switch in post-synaptic responses to GABA- and glycine-signalling from inhibitory to excitatory may contribute to over-excitation. Here, we investigated the expression pattern of the potassium/chloride co-transporter 2 (KCC2), a protein crucial for inhibitory neurotransmission in post-synaptic neurons, during disease progression in the SOD1 mouse model of ALS.
In the vulnerable hypoglossal nucleus of SOD1 mice, but not in the resistant oculomotor nucleus, KCC2 mRNA expression levels decreased by 62.5% between P40 and P130. Reductions in KCC2 immunoreactivity were observable beginning with P80 in the hypoglossal nucleus of SOD1-G93A mice. They first appeared in its ventral part, i.e. the genioglossal sub-nucleus, and then spread over the entire nucleus until P120. In addition, KCC2 immunoreactivity was no longer confined to the cell membrane, as seen in control mice, but was found more dispersed in the cytoplasm. Changes in KCC2 expression and localisation preceded tongue motility deficits which started at P110. Reductions in KCC2 expression levels and its intracellular distribution pattern may contribute to excitotoxicity by reducing and/or switching inhibitory synaptic input to excitatory. We currently develop an adult in vitro brainstem preparation for this mouse model to identify electrophysiological changes occurring in temporal association with disease with whole cell patch-clamp recordings.

Kategorie: Lecture

Rubrik: 9.Developmental Biology
Abstract Nr.:93

Titel:Expression of angiogenic growth factors during mesonephric glomerulogenesis

Autoren: De Spiegelaere W.(1),Cornillie P.(1),Van den Broeck W.(1),

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Abstract:
During mammalian embryogenesis, three successive excretory organs are formed in the course of renal development. The vestigial pronephros degenerates quickly and is followed by a mesonephros which is subsequently replaced by the metanephros that forms the definitive kidney. In certain species the mesonephros will develop into a fully working organ during a defined period of embryonic development. In the porcine embryo, the mesonephros is exceptionally large and functions during an extended period which continues far into the fetal stage. The basic filtration unit of both kidney types, i.e. the glomerulus, is very similar. The glomerular dimensions differ somewhat between the meso- and metanephros but their ultrastructure is remarkably similar. Because the mesonephros degenerates completely during development, this organ forms an interesting model for studying pathologic glomerular degeneration. The development and growth of renal glomeruli is regulated by the expression of specific angiogenic growth factors, including VEGF and the angiopoietins. The gene expression of these growth factors has been intensively studied in developing metanephric glomeruli but their expression during the growth of mesonephric glomeruli remains to be elucidated.
In porcine embryos, the presence of angiopoietins was studied immunohistochemically. Subsequently, gene expression of the angiopoietins and VEGF as well as their receptors Tie-1, Tie-2, VEGFR-1 and VEGFR-2 was analyzed by real-time RT-PCR on laser capture microdissected glomeruli. The gene expression during the initial glomerular development is similar to that observed in the metanephros. However, in contrast to metanephric glomerulogenesis, the angiopoietins remain upregulated during the later growth of the mesonephric glomeruli.

Kategorie: Lecture

Rubrik: 9.Developmental Biology
Abstract Nr.:94

Titel:Aspects of HOXA13, HOXD12 and HOXD mRNA expression in human development.

Autoren: Illig R.(1),Schwarzer C.(2),Fritsch H.(1),

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Abstract:
Our knowledge on Hoxa13, Hoxd12 and Hoxd13 expression during embryogenesis rely prevalently on animal models. We now investigated the expression of HOXA13, HOXD12 and HOXD13 in human tissue.
mRNA and protein distribution was examined by in-situ hybridization and immunohistochemistry on paraffin sections obtained from embryonal/fetal (5th - 12th week p.c.) and adult specimens.
Our data suggest temporally and spatially differential expression of HOXA13, HOXD12 and HOXD13 mRNA during human ontogeny. HOXA13 was detected in the rectal epithelium from 6th p.c., spreading towards the surrounding mesenchyme during 7th p.c.. Positive cells were observed in the epithelium of the stomach, kidney, urinary bladder, and perichondrium of limbs during 8th p.c.. HOXD12 appeared in the epithelium of kidney and urinary bladder and in the proximal perichondrium of extremities in 9th p.c.. Subsequent expression was evident in the rectal epithelium and surrounding mesenchyme (10th p.c.). HOXD13 positive cells were observed in the rectal epithelium in 7th p.c., in the surrounding mesenchyme at the end of 8th p.c. and in the distal perichondrial part of all limbs in 9th p.c.. In adults, significant expression of HOXA13, HOXD13 mRNA and rare HOXD12-positive cells were detected in most rectal layers.
Our results suggest a highly similar sequel of HOX gene expression in humans and rodents. This supports the idea of their crucial regulatory role in cell differentiation and proliferation also in human development and suggests some physiological functions also in adults.

Kategorie: Lecture

Rubrik: 10.Reproductive Biology

Abstract Nr.:95

Titel:Effects of LOX-1 and/or TLR4 activation by oxidized-low-density-lipoprotein (oxLDL) in granulosa cell subtypes

Autoren: Hueller H.(1),Vilser C.(1),Nowicki M.(1),Blumenauer V.(2),Hmeidan F.(2),Jogschies P.(2),Spanel-Borowski K.(1),

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Abstract:
Granulosa cell cultures derived from human follicle harvests express the lectin-like low density lipoprotein receptor (LOX-1) and respond by cell death-related autophagy under oxLDL stimulation (Dürrschmidt et al., 2006). We currently investigated the oxLDL dependent response of cytokeratin-negative (CK-) and cytokeratin-positive (CK+) granulosa cells. Pure CK+ and CK- cell cultures were treated with 150 µg oxLDL/ml under serum-free conditions for 12, 24 and 36 h. Protein extracts were studied by Western blotting for LOX-1, the Toll-like receptor 4 (TLR4), microtubule-associated-light-chain-protein 3 (LC3, autophagic marker) and cleaved caspase3 (apoptosis marker). The CK- cells underwent reparative autophagy under the oxLDL dependent LOX-1 activation. We found a shift from the LC3-I protein towards the LC3-II protein 36h after oxLDL treatment. The inhibition of the LOX-1 receptor impeded the up-regulation of LOX-1 and LC3-II protein. In respect to CK+ cells, they did not regulate LOX-1 expression under oxLDL, but increased TLR4 and CD14 production. Cell death, which was independent on cleaved caspase3 and LOX-1 activation, occurred under oxLDL. The inhibition of TLR4 changed the non-apoptotic cell death in an apoptotic form. Furthermore, in CK- cells, the inhibition of TLR4 down-regulated LOX-1 and induced apoptosis. We conclude that reparative autophagy occurs in oxLDL stimulated CK- cells through LOX-1 activation and in the presence of TLR4, whereas non-apoptotic cell death of CK+ cells is independent on LOX-1 and TLR4. TLR4 is protective in CK- cells. In CK+ ones, TLR4 mediates the non-apoptotic pathway (supported by the DFG Sp232/12-1.

Kategorie: Lecture

Rubrik: 11.Immune Biology
Abstract Nr.:96

Titel:CEACAM1 inhibits toll-like receptor 2-triggered anti-bacterial responses of human pulmonary epithelial cells

Autoren: Singer B.(1),Zabel S.(2),Riesbeck K.(3),Suttorp N.(2),Ergün S.(1),Slevogt H.(2),

Adressen:(1)Anatomy|University Hospital Essen|Essen|Germany; email:Bernhard.Singer@uk-essen.de; (2)Internal Medicine/Infectious Diseases and Pulmonary Medicine|Charite-Universitätsmedizin|Berlin|Germany; (3)Laboratory Medicine/Medical Microbiology|Lund University|Malmo|Sweden

Abstract:
Although Moraxella catarrhalis and Neisseria meningitidis are important human pathogens, they often colonize the respiratory tract without causing clinical symptoms. Both pathogens share the ability to bind specifically to CEACAM1 by expressing structurally unrelated proteins. The purpose of this work was to analyze the molecular mechanism, which orchestrates the shift of undamaging to destructive bacterial behaviour.
Expression of IL-8 and GM-CSF secreted by PBECs were evaluated with commercially available ELISA kits. Tyrosine-phosphorylations and co-immunoprecipitations of different proteins were determined by Western blot and Sandwich-ELISAs. Furthermore, luciferase activity assay was performed with the NF-kB-driven luciferase reporter plasmid system.
We found that ligation of CEACAM1 by UspA1 expressed on Moraxella catarrhalis or by Neisseria meningitis-specific Opa proteins reduced the TLR2-initiated NF-κB-dependent inflammatory responses of primary pulmonary epithelial cells. These inhibitory effects were mediated by tyrosine phosphorylation of the ITIM of CEACAM1 and the recruitment of SHP1. CEACAM1-recruited SHP1 was negatively regulating the TLR2-dependent activation of the PI3K/Akt pathway.
Our results show for the first time a novel strategy of pathogens to evade the immune response by CEACAM1-mediated inhibition of PI3K/Akt-dependent TLR2 activation. Thus, the CEACAM1-dependent immune-evasion strategy may guide to novel therapeutic strategies to combat infectious diseases.

Kategorie: Lecture

Rubrik: 11.Immune Biology
Abstract Nr.:97

Titel:Cilia-driven transport of particles and bacteria in the airways is preserved in the absence of mucus and control of periciliary fluid volume

Autoren: König P.(1),Bermbach S.(1),Schiemann F.(2),Petersen F.(2),Rupp J.(3),

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Abstract:
It is believed that cilia-driven transport of inhaled particles in the airways is dependent on a tight control of periciliary fluid volume and a continuous mucus layer. We used the model of the explanted submerged mouse trachea in combination with video microscopy to test whether this is indeed the case. In this model, the trachea is submerged resulting in an excess of periciliary fluid. Mucus was removed by repeated rinsing of the airway epithelium and its absence was confirmed by scanning electron microscopy. Despite the absence of the control of periciliary fluid volume and the mucus layer, a directed effective transport of polystyrene particles ranging from 4.5 to 20 μm was observed. This finding was also confirmed in human intrapulmonary bronchi. Smaller particles such as apathogenic bacteria that were added to the bath solution were also reliably transported. Destruction of ciliary function by overheating resulted in termination of transport of particles and bacteria. High speed video microscopy showed that particles were transported with maximal speed during the power stroke of cilia and with reduced speed during the recovery stroke. Particles and bacteria were also transported over areas with non-ciliated cells and without direct contact with cilia indicating that airway ciliated cells produce a continuous fluid flow that is sufficient for particle transport. In conclusion our experiments indicate that the effective transport of particles and bacteria in mouse and human airways is preserved in the absence of mucus and tight regulation of periciliary fluid.

Kategorie: Lecture

Rubrik: 11.Immune Biology
Abstract Nr.:98

Titel:Expression of IGF-I and IGF-II mRNA in various organs of a GH-overexpressing transgenic and wild-type tilapia: paradox reaction of the major immune organ spleen

Autoren: Eppler E.(1),Caelers A.(2),Mazel P.(1),Berishvili G.(1),Maclean N.(3),Reinecke M.(2),

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Abstract:
Several lines of GH-overexpressing fish have been produced and characterized concerning organ integrity, growth, fertility and health but few and contradictory data are available on IGF-I that mediates most effects of GH and nothing is known on IGF-II.
The expression of both IGFs in liver and various extrahepatic sites of adult transgenic (GH-overexpressing) tilapia and age-matched wild-type fish was determined by real-time PCR.
Both IGF-I and IGF-II mRNA were found in all organs investigated and were increased in gills, body kidney, intestine, heart, testes, skeletal muscle and brain of the transgenics (IGF-I: 1.4 to 4-fold; IGF-II: 1.7 to 4.2-fold). Except for liver, brain and testis the increase in IGF-I mRNA was higher than that in IGF-II mRNA. In pituitary, no significant change in IGF-I or IGF-II mRNA was detected. In spleen, however, IGF-I and IGF-II mRNA were both decreased in the transgenics, IGF-I mRNA even by the 19-fold. In agreement, in situ hybridisation revealed a largely reduced number of IGF-I mRNA-containing leukocytes and macrophages when compared to wild-type.
These observations may contribute to better understanding the reported impaired health of GH-transgenic fish. Growth enhancement of the transgenics may be due to the increased expression of both IGF-I and IGF-II in extrahepatic sites. It is also reasonable that the markedly enhanced expression of liver IGF-II mRNA that may mimick an early developmental stage is a further reason for increased growth.

Supported by the Swiss National Foundation (Project No. 118165)

Kategorie: Lecture

Rubrik: 13.COST B30 symposium
Abstract Nr.:99

Titel:Tail bud development and its stem cell properties in the mouse embryo

Autoren: Gajovic S.(1),Zizic M.(1),Mitrecic D.(2),Pochet R.(2),

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Abstract:
After gastrulation was completed, the further elongation of the vertebrate embryo is achieved through development of the tail bud. Whether the tail bud represents a stem cell blastema is still a metter of controversy.
The tail bud development and its stem cell properties were analyzed in mouse embryos (E11.5). Six markers of early cellular differentiation were tested for the presence in the tail bud: Oct4 and Sox2, early markers of stem cells; nestin, early marker of neural stem cells, Map2, marker of neurons, Gfap, marker of astrocytes, and Noto, marker of caudal notochord.
Morphogenetic movements in the wild type embryos revealed differentiation of the undifferentiated cells of the tail bud and formation of the neural tube in dorsal, and the notochord and the tail gut in the ventral portion of the region. The main result obtained was recognizing of Oct4 positive cells in the tail bud of the 11.5 days old mouse embryo. The very tip of the tail showed homogenous expression of Oct4 cells, while more cranial segment showed stronger positivity in cells at the periphery of the tail bud region. Segment in which was possible to recognize the medullary cord and the tail cord did not reveal Oct4 positive cells, confirming the presence of this protein only in the early step of differentiation.
Undifferentiated cells of the tail bud express stem cell marker Oct4. Tail bud differentiation is important for the development of tail structures.

Kategorie: Lecture