Symposium 7 - Development and plasticity

LOGISTICS OF BRAIN DEVELOPMENT

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The complex organization of the adult central nervous system is the end result of dramatic changes that occur during embryonic development i.g.: individual neurons are generated at specific time and place and than become allocated to final positions migrating along specific routes, while acquiring distinct biochemical makeup and establish synaptic connections.

To analyze role of cell lineage in the primate brain, we used recombinant retroviruses to label individual progenitor cells in the proliferative zones and follow the migration of their progeny as they assume their final positions. This complex process requires orchestration of multiple molecular events including selection of a pathway by cell recognition receptors, formation of adhesive interactions with cellular and extracellular substrates through multiple adhesion molecules and activation of specific ion channels and receptors that provide second messenger—mediated signals for the diverse cellular mechanisms involved in motility. We recently identified two polypeptides that form patchy microdomains at the plasmalemmal surface. Integrity of this junctional microdomains is maintained only during phase of cell migration and requires an intact microtubule. Using a acute cerebellar slice preparation in conjunction with calcium indicator dyes, we have learned that a combination of selective voltage—and ligand—activated ion channels may cooperatively regulate calcium influx into the migrating granule cell, and thereby control the rate of their movement essential for proper placement.

These results suggest that specific communications between heterogeneous classes of cells play a major role in establishing their position, identity, and selection of migratory pathways before they arrive at their final destination and form synaptic connections. New experimental approaches now allow examination of the role of individual molecular components that mediate these processes and provide new insight into the pathogenesis of heterogeneous migratory disorders of the cerebral cortex.

The different developmental rates of selected human brain structures

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Various rates of development and maturation are characteristic for particular structures of the central nervous system.
The differences of the maturing brain stem and telencephalon are evident in a routine neuropathological examination. The fetal archi- and neocortex reveals also uneven levels of maturation.

In order to precise those differences in humans we perform a morphological and morphometrical study on the dorsal vagal nucleus of medulla oblongata, on Ammon horn and on neocortex in fetuses between midgestation and birth. The numerical density of neurons, cell pericarya and nuclear cross-sectional area, ratio of nucleus to pericaryon area were measured. The results demonstrate gradual changes of decreasing cell density and segregation of neurons according to their size. They expressed the process of maturation which differs in rate in examined CNS structures.

The Formation of ON and OFF Pathways in the Developing Cat Retina is Regulated by Two Types of Activity-Mediated Events. Leo M. Chalupa, Neurobiology, UC Davis, CA 95616, U.S.A.

In all vertebrates the dendrites of ON and OFF retinal ganglion cells (RGCs) stratify in different sublaminae of the inner plexiform layer (IPL), so that cells signaling increments of light can be morphologically differentiated from cells signaling light decrements. At maturity ON and OFF RGCs are distributed in regular mosaic patterns across the retinal surface. We have been interested in unraveling the developmental factors that regulate the formation of such segregated ON and OFF RGC mosaic patterns in the developing cat retina. Evidence will be presented that this fundamental feature of RGC organization is regulated by two different types of activity-mediated events. Early in development RGC cell dendrites are multistratified. We have found that glutamate-mediated afferent activity provides the key signal for the normal retraction of RGC dendrites into ON and OFF sublaminae. This was demonstrated by the finding that intraocular injections of APB (which blocks the release of glutamate in rod bipolar cells and ON cone bipolars) arrests the stratification process. After the normal dendritic stratification is completed, the distribution of ON and OFF RGCs is much less regular than at maturity. We have found that at this stage of postnatal development the formation of regular mosaic patterns can be disrupted by intraocular TTX injections. Thus, Na-voltage gated activity serves to regulate the pattern of normal cell loss in the developing retina which gives rise to regular ON and OFF RGC mosaic patterns. (Supported by grants from the NIH and NSF.)

Spatio-Temporal Patterns of Ontogenetic Expression of Two Calcium Binding Proteins in the Superior Colliculi of Perinatal Laboratory Rats

B. Dreher, D.A. Barker, M.R. Bath and K.A. Keay - Department of Anatomy and Histology, University of Sydney, NSW, 2006, Australia.

Calcium binding proteins (CaBPs) participate in the regulation of intracellular calcium homeostasis in the mammalian central nervous system and could be used as markers of ontogentic neuronal maturation[1]. Using commercially available monoclonal antibodies against two CaBP - Calbindin D-28k or Parvalbumin and standard immunocytochemical techniques we were able to reveal two distinct spatio-temporal gradients of maturation of neurons located in the retinorecipient layers of the superior colliculi (SC) of Sprague-Dawley laboratory rats. The calbindin was expressed for the first time at postconceptional day (PCD) 20, that is 2 days before birth, by neurons located in the rostrolateral region of SC where supero-central retina (incuding the *area centralis*) is represented. In the next few days, the numbers of calbindin expressing neurons, as well as the spatial extent of the collicular zone containing them, increased substantially. However, only by PCD 29 the calbindin expressing neurons were present, as in adult rat, throughout the entire rostrocaudal and mediolateral extent of retinorecipient layers of SC. The spatio-temporal pattern of ontogenetic expression of calbindin appears to follow the spatio-temporal pattern of ganglion cell generation[2]. Furthermore, the period of onset of the ontogenetic expression of calbindin corresponds to the period of the naturally occuring ganglion cell death[3]. These correspondances in turn suggest, that the expression of calbindin in the SC relates to the establishment of the topographic maps of the retina in the SC. Furthermore, it appears that the spatio-temporal pattern of the onset of ontogenetic expression of calbindin reflects the spatio-temporal pattern of maturation of retinorecipient layers of SC postulated by "the temporal matching hypothesis" of Dreher and Robison[4].

By contrast, parvalbumin was expressed for the first time in the retinorecipient layers of SC at PCD 34 (12th postnatal day). In the next few days, the numbers of parvalbumin expressing cells increase substantially and by PCD 44 their numbers and distribution were adult-like. Thus, the timecourse of ontogenetic expression of parvalbumin corresponds to the period of refinement of corticotectal projections[5]. Monocular eye enucleation in newborn rat pups prevents the expression of parvalbumin in the SC contralateral to the removed eye. Unilateral ablation of visual cortex in newborn rat pups prevents the expression of parvalbumin in the SC ipsilateral to removed cortex. These results suggest that the ontogenetic expression of parvalbumin in the retinorecipient layers of the SC relates to the establishment of the corticotectal topographic map.

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FACTORS INFLUENCING DEVELOPMENT AND MATURATION OF FERRET SOMATOSENSORY CORTEX

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Since ferret kits are born with very immature nervous systems, over recent years this animal has been identified as a useful and interesting model for the study of neocortical development. Because of early cortical immaturity, our recent experiments were designed to further understand: (i) how the layers of the cerebral cortex are generated and form their final distribution in somatosensory regions and (ii) the development of intrinsic connectivity within the somatosensory cortex. We addressed these issues using live slices, organotypic cultures, and BRDU birthdating of cells populating the somatosensory cortex. A different series of animals were treated with MAM, a drug that prevents cell division during a specific period of time. This treatment, when appropriately timed can result in deletion of a specific layer of neocortex. Our studies on normal animals demonstrate that in very young brains (P 1-7) injections of dextrans label thin radial columns of cells including radial glia and neurons that extend from the ventricular zone into the cortical plate. Almost no processes extend from the labeled cells into the surrounding immature cortex, although axons can be traced toward the thalamus or opposite hemisphere. As the brain matures, dextran injections label neurons that extend processes laterally into the cortex and eventually form patchy connections in the upper layers. Although the label has an overall radial character in the older brains (P 14-28), the radial distribution is due to the pattern of individual dendrites, not columns of cells. BRDU birthdating of neurons in the somatosensory cortex indicates that although a substantial number of neurons are still migrating to the cortex, all layers have constituents present at the time of birth, even layer 2. Two groups of animals were treated prenatally with timed injections of MAM into the pregnant jill: (i) to affect subplate or early generated layers and (ii) to affect layer 4. Dextran injections into MAM-treated animals that deleted deep layers or subplate resulted in highly abnormal distributions of label into young animals (P 1-6). The radial character of radial glia and neurons was highly distorted in the young animals, suggesting that these layers may be important for early guidance. When layer 4 was deleted, the early pattern of dextran label was relatively normal, but later distributions (P14-28) were not typical in that the lateral distribution of fibers was delayed and normal patchy connections in the upper layers did not form.

LONG-LASTING EFFECTS OF NEONATAL SEROTONERGIC DEAFFERENTATION ON MORPHOLOGY AND ACTIVITY OF THE BARREL FIELD IN RAT.

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Recent papers (cf. J. Neurosci. 14:7594-7607) show that serotonin influences development of somatosensory cortex in albino rat. After neonatal lesion of serotonergic axons, at the age >60 days area of the barrel field was shrunk by about 20%. We checked these results on different (hooded) strain of rats and investigated the activity of barrels evoked by stimulation of the vibrissae in the 5-HT depleted rats. On the day of birth pups were pretreated with desipramine HCl and one hour later half of them received injection of 5,7 DHT. In one group unilateral vibrissectomy sparing row C was also performed. At the age of six weeks 2 rats of each group were processed for serotonin immunostaining. In rats injected with 5,7 DHT 70-90% of serotonergic fibers in the cortex were missing. 2-deoxyglucose mapping of the row C representation was done on remaining rats. The vibrissae were clipped on both sides with the exception of row C, the rats were injected with C^{14} 2-DG and had their vibrissae of the rows C on both sides stimulated. Autoradiograms of the brain sections cut tangentially to the barrel field were processed with an automatic system and the sections were Nissl-stained. Measurements of the size of barrels of the row C on the intact side showed that their linear dimensions in the 5HT depleted rats were 5-10% smaller than in the untreated littermates. The width of the activated zone on the autoradiograms was 10-20% smaller in these rats. Interestingly, neonatal vibrissectomy resulted in very large increase of cortical representation of the spared row C despite depletion of serotonin.

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Symposium 8 - Neuropeptides - from gene to regulation

PEPTIDERGIC NEURONAL PATHWAYS IN THE CENTRAL NERVOUS SYSTEM

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The existence and functional activity of over fourty neuropeptides in the central nervous system neurons have been investigated in the past two decades. A developing neuronal cell is genetically coded to synthesize even several neuropeptides and this ability is preserved during the whole life. Depending on the actual functional requirements, neuropeptides may exert neurotransmitter or neurohormonal functions, or participate in the restoration of damaged neuronal cells.

A summary will be given about such activities and gene expression of neuropeptides in several functional systems or pathways in the central nervous systems, like: hypothalamo-hypophyseal, central baroreceptor, hypothalamo-limbic, septo-hippocampal, stress-related nociceptive, olivo-cerebellar, extrapyramidal systems. The presence and the possible role of neuropeptides as co-transmitters in catecholaminergic, cholinergic and aminergic pathways will also be summarized.

Evidence for two peptidergic, analgesic defense systems at the spinal level.

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It is well established that peripheral axotomy induces marked changes in peptide levels in dorsal root ganglia and partly in the dorsal horn of the spinal cord. Thus, substance P (SP) and calcitonin gene-related peptide (CGRP) are downregulated and vasoactive intestinal polypeptide (VIP), galanin (GAL) and neuropeptide tyrosine (NPY) are upregulated. There are species differences in that SP and CGRP are downregulated and GAL upregulated in both rat and monkey, whereas upregulation of NPY and VIP occurs in rat but not in monkey. The mechanisms underlying this plasticity are not well understood, but growth factors and neuropoietic cytokines such as leukemia inhibitory factor (cholinergic differentiation factor) may play important roles. The synthesis, package and storage of these peptides have been analysed, and in most cases the peptides seem to be processed through the regulated secretory pathway, but there is also evidence that NPY after axotomy in some neurons may be directed into the constitutive pathway. Also peptide receptors are markedly regulated in response to axotomy. For example, marked changes have been observed in expression of mRNA for a NPY receptor, for the CCK_B receptor and for a neurotensin receptor. Thus sensory neurons undergo a dramatic change in phenotype in response to axotomy, presumably as an adaptation of the organism to the changes induced by nerve injury. In contrast, inflammation does not cause any upregulation of GAL, VIP or NPY in sensory neurons, but induces a marked increase in expression of several peptides in local dorsal horn neurons. Thus, nerve injury and inflammation, two paradigms leading to pain, activate different defense systems, one present in the sensory neurons themselves and the other localized to dorsal horn neurons.

Molecular anatomy of neuroimmune connection

E. Weihe (Marburg)

Not received

Implication of prohormone convertases in the precursor processing of neuropeptides, hormones and growth factors: experimental and developmental models of the central and peripheral nervous system. M. Marcinkiewicz, N. G. Seidah and M. Chrétien. Laboratory of Molecular Neuroendocrinology, Clinical Research Institute of Montreal, Montreal, QC, H2W 1R7, Canada. Supported by grant PG11474, MRC, Canada.

Active neuropeptides, peptide hormones and neurotrophic factors are produced via the processing of inactive precursor proproteins at pairs of basic amino acids. This limited proteolysis by endoproteases is thought to be both tissue- and precursor-specific and to be developmentally regulated. Furin, PC1, PC2, PACE4, PC4 and PC5 represent mammalian prohormone convertases (PCs) found in the endocrine, and central and peripheral nervous tissue, which cleave a number of precursors at basic residues normally processed in vivo. Typical bonds cleaved by PCs include the pairs Lys-Arg; Arg-Arg; Lys-X-Lys/Arg-Arg and less frequently Lys-Lys; single Lys and single Arg. These consensus sequences were demonstrated using different precursors as models, including proopiomelanocortin (POMC), proinsulin and neurotrophin NGF, BDNF and NT-3 precursors, which have been studied in cell lines. Using the in situ hybridization we localized the sites of PCs mRNA expression together with the expression sites of different precursors. This include the ontogeny studies in the primordia of the brain and pituitary, and pancreatic islets in which we compared the expression of PCs with that of POMC and proinsulin, respectively. In the experimental model of epilepsy in which the epileptiform activities were provoked by kainic acid administration, or pilocarpine administration, we observed a transient expression of PCs, similar to that of NGF and BDNF. Finally, the involvement of furin and PC1 in the processing of proNGF was deduced from the studies on their co-expression in the distal stump of lesioned sciatic nerve. In conclusion, we propose that under different stimuli the activation of different precursors is performed by a unique cocktail of convertases each of which either alone or in combination with others act to process inactive precursors and thereby playing an important role in development and in the plasticity of the neuronal system.

NEUROPEPTIDE Y (NPY) AND ITS mRNA IN DISCRETE BRAIN AREAS AFTER CHRONIC ADMINISTRATION OF NEUROLEPTICS

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It is well known that pharmacological effects of neuroleptics (NL) are elicited mainly by the blockade of dopaminergic receptors. It was shown in last years that these drugs can affect peptidergic neurons in the brain. In this presentation the level of NPY in discrete rat brain areas after ip administration of neuroleptics (single inj. 14, 28 days) is described. The most evident changes were observed 14 days after NL administration. In hypothalamus chlorpromazine (2 or 10 mg/kg), haloperidol (0.5 or 2 mg/kg) increased NPY level whereas sulpiride (50 or 100 mg/kg) or clozapine (10 or 25 mg/kg) had no effects. In nucleus accumbens all studied NL diminished NPY level. The level of NPY mRNA was measured in this area after haloperidol and clozapine administration. This level was diminished. All studied NL has not affected NPY level in hippocampus and striatum. Interactions between studied NL quinpirole (D_2 agonist), or SKF 38393 (D_1 agonist) or SCH23390 (D_1 antagonist) and studied NL were shown. All data indicate that the changes in NPY level in some discrete areas of brain elicited by NL depends upon the blockade of D_1 as well as D_2 receptors.

EFFECTS OF DRUGS OF ABUSE ON THE PRODYNORPHIN SYSTEM ACTIVITY IN THE RAT BRAIN

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Pharmacological data indicate that prodynorphin peptides and exogenous κ agonists modulate some effects of drugs of abuse. In order to elucidate the involvement of the endogenous prodynorphin system in the mechanism of drug dependence, we investigated the effect of morphine, cocaine, amphetamine and ethanol administration on the α-neoendorphin tissue level, its in vitro release, and the prodynorphin mRNA in the rat brain. The present study showed that repeated, but not single, admnistration of those substances enhanced the prodynorphin system activity in the nucleus accumbens and, to a lesser extent, in the caudate putamen at 24 or 48 h after the withdrawal of drugs. Considering the fact that prodynorphin peptides mediate aversive effects, the above changes may be of functional significance for the symptoms of the drug withdrawal.

OPIOID SYSTEMS IN WAG/Rij RATS - A GENETIC MODEL OF ABSENCE EPILEPSY

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The role of endogenous opioid systems in regulation of the epileptic activity in WAG/Rij rats, a genetic model of absence epilepsy, was investigated. A pharmacological experiments showed that agonists of the μ receptor increased the epileptic activity in WAG/Rij rats, whereas κ agonists had an antiepileptic effect in that model. Biochemical studies demonstrated an increase in the cortical and striatal proenkephalin biosynthesis. Since proenkephalin-derived peptides induce absence-like seizures, elevation of the proenkephalin system activity, accompanied with a decrease in the cortical prodynorphin biosynthesis, may be functionally linked to the occurrence of an epileptic activity in this strain of rats.

LIGANDS FOR NEUROPEPTIDE RECEPTORS

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We are now witnessing revolutionary progress in neuropeptide research. In the last several years a number of endogenous peptides generated by neurons have been newly recognized and isolated. Cloning and characterization of neuropeptide receptors are now almost routine. Physicochemical and mathematical methods have allowed modelling of the active conformations of neuropeptide ligands during their interaction with receptors. Together, these powerful methods have set the stage for the creation of new potent and selective peptide analogues as well as peptide mimetics. Because of their potential ease of large-scale synthesis, relative stability, and bioavailability trough the oral route, non peptide ligands have become the goal of many medicinal chemists currently engaged in structure-activity relationships (SAR) studies of neuropeptides. We will survey SAR of several prototypical classes of neuropeptides include, the endogenous opioids, the tachykinins, angiotensin II, oxytocin, vasopressin, and cholecystokinin. Although medicinal chemists are fascinated by the possibility of creation of non-peptide ligands for neuropeptide receptors, most currently available nonpeptide ligands for neuropeptide receptors were found, not as a results of SAR study, but through large-scale biological screening of available organic compounds.

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THE CONTRIBUTION OF AT_1 AND AT_2 ANGIOTENSIN RECEPTORS TO ITS COGNITIVE EFFECTS

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Two distinct angiotensin receptor subtypes, designated AT_1 and AT_2 have been identified basing on their differential affinity to selective antagonists losartan and CGP 42112A (CGP), respectively. In this study I attempted to assess the role of the both angiotensin receptor subtypes in certain cognitive effects of AII and AII(3-7) using the antagonists in behaviorally inactive doses. Losartan (1 μg), CGP (2 μg), AII (1 nmol) and AII(3-7) (1 nmol) were dissolved in saline and given intracerebroventricularly (icv) as 2 μl injections. First injection was given to the left, and second 5 min later, to the right cerebral ventricle. A minimum of 10 subjects were in each group. There were six groups receiving the following (left-right) icv injections; control (saline-saline), losartan (losartan-saline), AII (saline-AII), losartan -AII (losartan-AII), AII(3-7) [saline-AII(3-7)] and losartan-AII(3-7) [losartan-AII(3-7)]. In another six groups losartan was replaced by CGP. Effects of these injections upon several aspects of memory were then tested. Retention of passive avoidance was evaluated in one-trial step-through situation in animals given the 2nd icv injection 15 min before the test trial. Acquisition of conditioned avoidance responses (CARs) was tested during 5 daily 20 trial sessions, first session commencing immediately after the 2nd icv injection. Object recognition was tested in a standard plastic box. AII and AII(3-7) significantly improved retention of the passive avoidance and recognition, and these effects were abolished by both, losartan and CGP. Better, after AII and AII(3-7), acquisition of CARs was unchanged by losartan. None of the treatments significantly changed behavior of rats in the open field. The results point to the involvement of AT_1 and AT_2 receptors in memory enhancing action of angiotensins.

Symposium 9 - Pharmacological modulation of memory

PHARMACOLOGICAL MODULATION OF MEMORY - INTRODUCTORY REMARKS

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Similarly to several higher nervous functions, memory may be manipulated pharmacologically. While it is not difficult to impair memory, its improvement is not easy. Studies on conditions leading to deterioration of memory were particularly important for establishing the role of cholinergic system and formulation of the cholinergic hypothesis of memory. Moreover, animals with pharmacologically-induced memory deficits are often used as models for testing procognitive properties of drugs. A plethora of compounds described as potential procognitive drugs and virtual absence of drugs definitely improving memory, particularly in cases of serious impairment, indicates that the problem is still open. The difficulties in finding procognitive drugs result from the lack of appropriate model, lack of standard procognitive drugs, lack of theory of procognitive action, and the complexity of memory, which includes various types of memory (e.g., declarative vs. operative) and various processes involved in memory and learning (e.g., acquisition, storage and retrieval). Particularly important seems to be the experimental setup in which motivation for learning is not achieved by starvation or cruel punishment, so that the results may be generalized for ordinary human population. Effective procognitive drugs may act not directly on the memory process, but on the level of alertness (psychostimulants) or the blood supply and metabolism of nervous and glial tissue (calcium blockers). Several classes of procognitive (nootropic) drugs were found possibly effective in improvement of cognitive performance in normal humans or in mild age-related memory deficits; the effectiveness of the procognitive drugs seems to decrease with the increase of degree of memory impairment. Nevertheless drugs of several classes (piracetam-like nootropics, drugs activating cholinergic transmission, benzodiazepine reverse agonists, drugs affecting cerebral circulation, psychostimulants, etc.) are extensively investigated and some optimistic findings are reported.

The Basal Forebrain and Memory: Influence of Drugs and Aging

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The basal forebrain region includes a population of acetylcholinergic neurons that lie within the medial septum, vertical and horizontal limbs of the diagonal band of Broca and the nucleus basalis magnocellularis (NBM). Basal forebrain lesions impair performance in a variety of behavioral tasks. Recent studies have raised doubts about the precise role of NBM cholinergic cells in the performance of these tasks. It was once believed that NBM cholinergic cells influenced learning and memory. However, the basal forebrain cholinergic system may be more involved in controlling attention and vigilance. I have used a selective immunotoxin to destroy NBM cholinergic cells in the basal forebrain of rats. These rats were tested in an operant task that is sensitive to impairments in attentional abilities. In addition, I have investigated the effects of anti-cholinergic drugs upon performance in this task. The results show that basal forebrain cholinergic lesions impair attentional ability in both young and old rats. I have also investigated the ability of selected drugs to provide neuroprotection for NBM cholinergic cells when exposed to excitatory amino acid neurotoxins. This work was supported by the National Institute of Aging, R01 AG10546, and Merz GmbH+Co, Frankfurt, Germany.

IN VITRO STUDIES WITH AMPA AND NMDA RECEPTOR ANTAGONISTS AND MODULATORS ON SYNAPTIC TRANSMISSION, LTP AND EXCITOTOXICITY - IMPLICATIONS FOR THERAPEUTIC SAFETY.

Chris G. Parsons, Tadeusz Frankiewicz, Sabine Hartmann, Gerhard Rammes. Merz + Co., D-60318 Frankfurt am Main 1, Germany

Glutamate is the major excitatory neurotransmitter in the CNS. AMPA receptors are involved in most forms of glutamatergic transmission whereas NMDA receptors have a more selective role in mechanisms underlying the induction of synaptic plasticity. Unfortunately, over activation of NMDA receptors underlies the excitotoxic effects of glutamate in many pathological conditions. The development of safe therapeutic agents has been hindered by the fundamental role of glutamate receptors in physiological processes as neuroprotective doses are often very close to those causing side effects. However, there is recently a renaissance of interest in modulators of glutamate receptors as therapeutic agents. Thus, low affinity uncompetitive NMDA receptor antagonists may have a better profile due to their fast, voltage-dependent open channel blocking kinetics and glycine$_B$ antagonists may selectively effect the pathological activation of NMDA receptors by reintroducing receptor desensitisation. Agents such as aniracetam, cyclothiazide and AMPAkines have been shown to enhance synaptic plasticity by slowing AMPA receptor desensitisation. They may therefore be useful in the symptomatological treatment of cognitive deficits in e.g. Alzheimer's disease but could also speed the progression of such diseases by enhancing excitotoxicity. This presentation will show our data comparing the effects of such agents on synaptic transmission and LTP in hippocampal slices and agonist-induced currents in various cell cultures with neuroprotective activity in the same preparations. The aim of these studies was to assess the validity of determining *in vitro* "therapeutic indices" for these substances as a predictive model for their therapeutic profile in *in vivo* models and to gain insights into the importance of factors such as fast open-channel block and receptor desensitisation in this regard.

NEUROCHEMICAL CORRELATES OF MEMORY RETRIEVAL: CHOLINERGIC AND GLUTAMATERGIC INTERACTION

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Cholinergic and glutamatergic systems of the hippocampus are both believed to be engaged in learning and memory processes, but the exact nature of their involvement is still unknown. Both of them are involved in spatial learning, which is impaired by cholinolytics and N-methyl-D-aspartate (NMDA) antagonists. To find out whether memory retrieval and forming of a memory trace are associated with the cholinergic system of the hippocampus, the responsiveness of phospholipase C linked cholinergic system of the hippocampus was investigated in rats trained in the Morris water maze. The responsiveness of the cholinergic system was measured by an increase in the accumulation of inositol phosphate in the hippocampal slices, induced by exposure to carbachol. We have found that in the rats which swam to the platform placed in already known position (memory retrieval), the accumulation of inositol phosphate transiently increased above the values observed in handled controls and rats which had to seek the platform placed in the new position (memory retrieval plus acquisition of a new information), and this increase was strongly inhibited by NMDA. This result suggests that memory retrieval rather than formation of a memory trace, is related to increased responsiveness of hippocampal cholinergic system, and that formation of new memory trace, which updates the long-term memory, inhibits this cholinergic activation, most probably by learning-associated increase in NMDA receptor activation.

THE ROLE OF THE GLUTAMATERGIC SYSTEM IN LEARNING AND MEMORY - BEHAVIOURAL STUDIES

W. Danysz[1], W. Zajaczkowski[1], M. Misztal[1] and G. Wenk[2]
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It has been suggested that NMDA receptor antagonists may have neuroprotective activity in some chronic neurodegenerative diseases believed to involve glutamate excitotoxicity. However, since NMDA receptor antagonists are expected to inhibit learning processes, the potential impairment of cognition needs to be taken into account. This is particularly relevant for neurodegenerative dementia where a drastic worsening of the symptoms might be anticipated. Hence the crucial question is: is it possible to achieve neuroprotective activity without the risk of learning disruptions. Our studies in rats suggest that in some "models" of excitotoxicity, neuroprotective effects of NMDA receptor antagonists (MK-801, memantine) are observed far below the dose range expected to impair learning. This refers in particular to protection of cholinergic NBM neurons under conditions of either acute or chronic application of a direct NMDA receptor agonist. Traditionally NMDA receptor antagonists are expected to inhibit learning and activation of NMDA receptors (or positive modulation) to improve cognitive processes. However, the NMDA receptor should be viewed as a translator reacting in a qualitative way to a temporal input due to voltage dependent Mg^{2+} block. Thus, both inhibition and overstimulation of these receptor may produce cognitive deficits by decreasing the signal to noise ratio. In line with this assumption NMDA receptor stimulation at non-toxic doses impairs learning. This impairment was attenuated by the NMDA receptor antagonist memantine supporting the specificity of the observed effect.

LOCUS COERULEUS ACTIVITY IN BEHAVING RATS: A CLUE TO THE ROLE OF NORADRENALINE IN MEMORY.

Susan J. SARA, Inst. Neurosciences, CNRS, Univ P & M Curie, 9 quai St Bernard 75005 Paris, FRANCE

Noradrenaline (NA) acts at ubiquitous postsynaptic targets to modulate the mode of firing and excitability of cells, as well as to gate responses to sensory stimuli and promote long term potentiation. Thus the timing of firing of locus coeruleus (LC) neurons and consequent release of NA should be of fundamental importance for information processing and memory. We record single LC units in controlled behavioral situations, in order to relate LC activation to specific behavioral contexts. LC cells respond in burst to novel auditory stimuli, or to novel objects encountered during free exploration with rapid habituation. When a stimulus is then associated with reinforcement, there is a renewed response, which is transient. During extinction, LC neuronal responses reappear. Thus, LC cells respond to novelty or change in incoming information, but do not have a sustained response even when stimuli have a high biological significance.

We have recently found a small population of frontal cortex neurons which exert an inhibitory influence on LC activity and these could be responsable for the plasticity in firing of LC neurons as a function of the changing significance of the stimulus.

The gating and tuning action of NA released in target sensory systems at the critical moment of change would promote selective attention to relevant stimuli.. Selective long term storage may occur as a function of the degree of LC activation, perhaps through a permissive role of NA on LTP mechanisms.

Plenary lectures

Cholinergic mechanisms in brain pathology
A. Szutowicz, Gdańsk

Not received

Modulatory actions of co-transmitters in *Aplysia*: cellular mechanisms of action and functional implications
K. Weiss, New York

Not received

Polish Neuroradiology today

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Author presents actual state of polish neurobiology, and its advances in the last twenty years (1975-1995). The beginning of these two decades has been characterized by the intense development of many neuroradiological methods, namely CT, TCD, nuclear medicine and lately MRI. These methods, widely available in western countries, spread in Poland with a few years' delay, mainly due to economic reasons: unfortunately high technology (in medicine as well) requires high costs. Despite economical limitations mentioned above, our neuroradiology introduced new methods and trends. They include the use of dynamic examinations in assessment of regional brain perfusion. Dynamic CT with use of iodinated contrast media and/or xenon is a method just as useful as a nuclear study. Evaluation of brain perfusion is also possible by a non-invasive study such as TCD. the first transcranial doppler equipment has been introduced in late eighties. Today it is a widely available diagnostic method. Introduction of MRI and helical CT are unquestioned breakthroughs in neuroimaging. MRI is a useful tool in neuroendocrine disorders, providing solutions that are beyond diagnostic possibilities of laboratory tests. Author's lecture will be concerned with the new trends in neuroradiology, in research and daily clinical practice.

CT AND MR IN DIFFERENTIAL DIAGNOSIS OF DEMENTIA

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This study was carried out to evaluate CT and MR usability in differential diagnosis of dementia.

The material comprised 88 demented patients clinically diagnosed as dementia of Alzheimer type (DAT)-49 cases, multiinfared dementia (MTD)-21 cases and mixed cases (MIX)-17 patients. Location, extend and morphology of brain lesions (leukoaraiosis, focal changes, while matter hiperintensitios) and cerebral atrophy in CT and MR were evaluated in each case. Results were compared with clinical findings. Statistical analysis was based on Quinlenn's method.

CT and MR findings were the same in all analysed types of dementia but their frequency and extend was significantly different. Sensitivity (SE) of the method was 0.82 and specificity (SP) was 1.0 for DAT cases. Analogically SE 0.81, SP 1.0 for MID and SE 1.0, SP 0.81 for MIX.

CT and MR is a high sensitive and specific method for dementia differentiation however racognition of dementia is impossible without clinical data.

MAGNETIC RESONANCE IMAGING IN DIAGNOSING AND TREATMENT MONITORING OF MULTIPLE SCLEROSIS

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The authors present their experience with 277 cases of multiple sclerosis (171 women and 106 men aged from 11 to 66 years). 83 patients took part in a double-blind placebo-controlled trial of a new immunosuppressive drug 2-CDA (2-chloro-2-deoxyadenosine).

17,8% of all cases showed the signs of the acute phase of MS - oedema around the plaques and contrast enhancement with Gd-DTPA as a result of increased blood-brain barrier permeability. These signs allow to estimate disease activity which turned out to be different clinically and radiologically. White matter hyperintensities were found most frequently in periventriculat white matter (in 100% of cases), in subcortical localization (52,2%) and in the corpus callosum (44,4%). 37% of all cases were accompanied by cortical brain atrophy. Subcortical brain atrophy was less frequent (16,7%). In 64,9% of cases the corpus callosum atrophy was found.

MRI is now accepted as a tool of monitoring disease activity during experimental therapies. Patients from the placebo group turned out to be compliant to any changes of the plaques (increase/decrease of the number/size of plaques) - chi^2 = 0,01096. Decrease of the plaques' size after 2-CDA treatment was found mainly in women. No correlation between age of the patients and plaques' changes has been established.

MR IMAGING OF THE CRANIAL NERVES

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The presentation explores clinical indications, limitations and the rationale for use of Gs-DTPA in MR imaging of the cranial nerves. The pertinent anatomy of the cranial nerves as well as the structural lesions that produce the symptoms of trigeminal neuralgia, hemifacial spasm, Bell's palsy and glossopharyngeal neuralgia are reviewed.

Correlation between the clinical presentation of trigeminal neuralgia and the MR findings is discussed. Special attention has been paid to the evaluation of vascular compression at the root entry/exit zone. Own experience in 60 examinations is presented. The possible significance of the method for a preoperative estimation of cranial nerves and the advantages of MRI over other imaging methods are outlined.