P6.17 **KAPPA$_3$ OPIOID ANALGESIA**

Grazyna Ciszewska, Gavril W. Pasternak
The Cotzias Laboratory of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center and Depts of Neurology & Neuroscience and Pharmacology, Cornell U. Medical College, New York,U.S.A.

Novel opioid drugs have provided major tools in understanding opiate actions. Since the first suggestion of the kappa receptors by Martin, many groups have searched for kappa binding sites. We synthesized NalBzoH (6-desoxy-6-benzoylhydrazino-N-allyl-14-hydroxydihydronormorphinon) which is a novel opiate with potent action at both mu and kappa receptors. In binding studies ^{3}H-NalBzoH labels mu receptors quite potently as well as a discrete population of sites with a unique binding profile termed kappa$_3$. The density of kappa$_3$ receptors in rat, mouse and calf brain are 2-fold higher than mu and delta receptors. In vivo, NalBzoH potently reverses morphine actions, consistent with antagonist activity at mu receptors. However, given alone NalBzoH is a potent analgesic acting through supraspinal mechanisms. This analgesia is resistant to selective antagonists against mu (β-funaltrexamine), delta (naltrindole) and kappa$_1$ (nor-binaltorphimine) receptors. Furthermore, NalBzoH analgesia was not cross tolerant to mu or kappa$_1$ analgesics. On the other hand NalBzoH and nalorphine analgesia were cross tolerant, implying that kappa$_3$ receptors represent the nalorphine, or "N", receptors first proposed by Martin over 25 years ago.

Inhibition of the Nociceptive Trigemino-Hypoglossal Reflex by Nicotine in Rat. P6.18

M.Łuczyńska, E.Strumiłło-Dyba and W.Z.Traczyk

Department of Physiology, Institute of Physiology and Biochemistry, Medical University of Lodz, Poland.

The investigations of Substance P (SP) distribution in central nervous system have demonstrated presence of this peptide in the structures mediating pain sensation. The reduction of the SP-immunoreactivity in different regions of central nervous system after i.v. nicotine administration has been demonstrated.

Our previous experiments have shown specific effect of the active SP fragment in nociceptive trigemino-hypoglossal reflex.

The present study was aimed to examine possible influences of nicotine on intensity nociceptive trigemino-hypoglossal reflex. Experiments were performed on male rats in chloralose anaesthesia. In the animals the amplitude of movements of stretched tongue evoked by incisor pulp stimulation before and after i.v. injection of 0,8 mg/kg nicotine was recorded. Nicotine induced significant decrease of amplitude of trigemino-hypoglossal reflex. This results might be demonstrated a further link beetwen pain sensation and SP-ergic neurones.

Plenary lectures

L3 K+ CHANNELS: STRUCTURE, REGULATION, MOLECULAR PHARMACOLOGY AND INVOLVEMENT IN DISEASE STATES

M. Lazdunski, Sophia Antipolis

See page 196

Salt-appetite, its neuroendocrine basis L4

Eliot Stellar
University of Pennsylvania

Based on the early work of Richter (1936), showing that the adrenalectomized rat kept alive by drinking hypertoric NaCl solutions, Epstein & Stellar (1955) demonstrated that salt appetite was not dependent on learning. A series of papers by Epstein and his students made clear that in addition to the adrenal steroid, aldosterone, salt appetite depended upon the action of angiotensin II in the brain. Blocking either hormone in the brain reduced depletion induced salt appetite in half; blocking both eliminated it. Two or three salt depletions enhanced salt appetite by nearly a factor of two, even when the rats never had a chance to drink salt in the first depletion. With multiple depletions, need-free salt intake also increased when the rats were replete, producing an elevated chronic salt appetite. Strikingly, female rats drink almost twice as much as males and become more enhanced. The neural circuitry involved in the synergy of angiotensin and aldosterone is becoming clearer with lesions of the amygdala that reduce aldosterone's effects and lesions of the anterior wall of the third ventricle that reduce angiotensin effects. The significance of salt appetite in nature, in body fluid homeostasis, and in blood pressure is discussed.

Symposium (S4) - Excitatory amino acids: basic aspects and therapeutic expectations

S4.1 MULTIPLE INTRACELLULAR SIGNALS OF GLUTAMATE RECEPTORS: BIOCHEMICAL STUDIES IN PRIMARY NEURONAL CULTURES

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Glutamate receptors may be subdivided on the basis of signal transduction mechanisms into ionotropic receptors, which are coupled with ion channels, and metabotropic receptors which activate effector enzymes and enhance the formation of intracellular second messengers. Primary cultures of granule cells from cerebella of neonatal rats express several glutamate receptor subtypes allowing us to study their intracellular signal transduction mechanisms in a homogeneous population of neurons. The activation of ionotropic *N*-methyl-D-aspartate (NMDA)-sensitive receptors leads to increased Ca^{2+} influx followed by a cascade of intracellular events including the activation of phospholipase A_2, phospholipase C (PLC), and protein kinase C. NMDA receptor activation enhances also the activity of nitric oxide (NO) synthase. Thus generated NO may serve as an intracellular or extracellular messenger causing the activation of soluble guanylate cyclase and the ensuing cyclic GMP formation, as well as, the enhancement of endogenous ADP-ribosyltransferase activity leading to covalent modifications of specific, possibly GTP-binding, proteins. The multiple Ca^{2+}-dependent signals generated by NMDA receptor activation may allow a selective targeting of the receptor-induced signal at specific intracellular effectors.

Cerebellar granule cells express in culture several subtypes of metabotropic glutamate receptors (mGluR). One subtype, mGluR1, is coupled through a G protein to PLC and its activation causes the generation of two second messengers inositol-1,4,5-trisphosphate and diacylglycerol. The expression of this receptor mRNA is modified developmentally and in response to modified culture conditions. In addition, changes in culture conditions promote the expression of pharmacologically distinct PLC-coupled mGluRs, differing by their sensitivity to the mGluR agonist *trans*-1-amino-1,3-cyclopentanedicarboxylic acid and the noncompetitive antagonist 2-amino-3-phosphonopropionate. A distinct metabotropic receptor (mGluR2) is coupled in granule cells to the inhibition of adenylyl cyclase. This coupling, via a pertussis toxin-sensitive G protein, can be demonstrated in granule cell membranes. These data indicate the existence, in primary cultures of cerebellar granule cells, of a functionally heterogeneous family of G protein-coupled metabotropic glutamate receptors.

S4.2 CELLULAR ELECTROPHISIOLOGICAL STUDIES ON NONCOMPETITIVE NMDA AND NON-NMDA ANTAGONISTS: IMPLICATIONS FOR NEUROLOGICAL THERAPEUTICS

Michael A. Rogawski, Neuronal Excitability Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA

Excitatory amino acid antagonists have therapeutic potential in a diverse group of neurological disorders, including the epilepsies, various forms of neurodegeneration and Parkinson's disease. In this regard, there has been particular interest in phosphonic acid competitive NMDA recognition site antagonists, and more recently in quinoxaline competitive non-NMDA (AMPA/kainate) antagonists. However, noncompetitive antagonists have the advantage that their blocking action is not overcome by high levels of glutamate, as may occur during seizures or in glutamate-induced excitotoxity.

In whole cell voltage-clamp recordings from cultured rat hippocampal neurons, the MK-801/carbamazepine-analog ADCI was found to antagize NMDA responses in a use-dependent and voltage-dependent fashion, indicating that it is an open channel-type noncompetitive NMDA antagonist. ADCI has a broad spectrum of anticonvulsant activity in animal seizure models and protects against the development of kindling, but has a higher therapeutic index than most other NMDA antagonists.

The novel 2,3-benzodiazepine GYKI 52466 has been reported to antagonize non-NMDA receptor mediated responses, and to have anticonvulsant and neuroprotective activity. Voltage-clamp recordings demonstrated that GYKI 52466 is a highly selective antagonist of kainate and AMPA induced currents in hippocampal neurons. The blocking action of GYKI 52466 occurred in a noncompetitive fashion with respect to kainate and AMPA, was voltage-independent and falled to show use-dependence, indicating a novel allosteric blocking mechanism.

Noncompetitive excitatory amino acid antagonists such as the NMDA antagonist ADCI and non-NMDA antagonist GYKI 52466 could offer advantages over competitive antagonists in the treatment of glutamate-associated neurological disorders, particularly under conditions where high levels of the amino acid would render competitive antagonists relatively ineffective.

S4.3 EFFECT OF A SELECTIVE METABOTROPIC EXCITATORY AMINO ACID RECEPTOR AGONIST ON cAMP ACCUMULATION.

PILC. A., FRANKIEWICZ. T. and LEGUTKO. B.
INSTITUTE OF PHARMACOLOGY POLISH ACAD. SCI., 31-343 KRAKOW, SMETNA 12, POLAND.

Excitatory amino acids (EAA) stimulate both ionotropic and metabotropic receptors. There are several data that metabotropic receptors are coupled to phospholipase C, much less is known about effects of EAA on cyclic AMP accumulation. In this study we describe the effect of a selective agonist metabotropic receptors trans-1-aminocyclopentane-1,3-dicarboxylic acid (trans-ACPD) on noradrenaline or forskolin stimulated cAMP accumulation in slices from rat cerebral cortex. Trans-ACPD produced a small increase in basal cAMP accumulation and greatly (4 fold), in a dose dependent manner enhanced the cAMP response to noradrenaline. This enhancement was dose-dependently inhibited by the metabotropic EAA receptor antagonists L-2-amino-3-phosphonopropionic acid (L-AP3) and L-2-amino-4-phosphonobutyric acid (L-AP4). The third effect of trans-ACPD was a dose dependent inhibition of forskolin-stimulated cAMP accumulation. The results indicate, that multiple metabotropic receptors for EAA coupled to adenylate cyclase may exist.

S4.4 BEHAVIOURAL EXPRESSION OF GLUTAMATERGIC FUNCTION - FOCUS ON BASAL GANGLIA

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Glutamate is a main transmitter in the cortico-striato-thalamo-cortical-loops. The behavioural effects of glutamate (mediated via NMDA receptors) in the striatum is opposite to that of dopamine (mediated via D2 receptors). Thus, blockade of the glutamatergic transmission, either by lesions or by NMDA-antagonists, induces psychomotor stimulation (in the rat, locomotion and continuous sniffing). In dopamine deficiency states, behaviourally expressed as akinesia and rigidity (catalepsy), there is a relative overactivity of the glutamatergic system (in the striatum, the subthalamic nucleus and its efferent connections) which can be effectively counteracted by NMDA-antagonists. Antagonists at the different binding sites of the NMDA receptor show different behavioural and biochemical profiles.
Agonists at the NMDA receptor, such as NMDA, reduce spontaneous behaviour and potentiate catalepsy.
Non-NMDA receptors are differently involved in the control of behaviour.

Supported by the DFG and by the BMFT.

S4.5 GLUTAMATE, LONG-TERM POTENTIATION AND MEMORY

Klaus G. Reymann

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Long-term potentiation (LTP) of synaptic responses is a model used for the investigation of cellular mechanisms of memory formation. According to our three-stage hypothesis of LTP, the Ca2+/Calmodulin-dependent induction is followed by protein kinase C (PKC)-dependent intermediate and late protein synthesis-dependent stages. Here we investigated with extracellular techniques in the CA1 region of hippocampal slices the involvement of different glutamate receptors in the induction and maintainence of LTP. NMDA receptor activation during tetanization is an essential condition for all 3 stages of LTP. Our data suggests that in contrast to NMDA-receptors metabotropic Qp receptors and the subsequent activation of protein kinase C are involved in mechanisms enabling only the late stages of LTP.

The sensitivity of potentiated neurons to test pulses of the iontophoretically-applied quisqualate receptor ligand _-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) slowly increases after tetanization. This delayed increase in agonist sensitivity is prevented by both the NMDA-antagonist APV and the protein kinase inhibitor K-252b. This data suggests that LTP is maintained initially (0-30 min) by a presynaptic mechanism and than by a postsynaptic mechanism or by both pre- and postsynaptic mechanisms. The increased postsynaptic sensitivity of ionotropic glutamate (AMPA) receptors might be due to a posttranslational transformation of the receptor-ionophor complex or expression of new AMPA-receptors.

The possible involvement of such mechanisms in memory processes will be discussed.

S4.6 THE ROLE OF CALCIUM IN GLUTAMATE-MEDIATED TOXICITY

Jerzy W. Łazarewicz
Medical Research Centre, Pol. Acad. Sci., Warsaw, Poland

The physiological importance of calcium in glutamatergic signal transduction and its pathogenic role in glutamate neurotoxicity is well documented and generally accepted. Glutamate and calcium may be involved in several brain disorders, leading in ischemia to neuronal damage in susceptible regions such as the hippocampal CA1. Evidence from studies of animal models of global cerebral ischemia indicate that calcium ionophores induced by the NMDA-sensitive glutamate receptors represent the major pathway of calcium influx into hippocampal neurons during ischemia, whereas the L subtype of voltage-sensitive calcium channels seem to be less important in this phenomenon. In vivo studies have revealed that the maximal capacity of calcium ionophores induced by glutamate receptor agonists greatly exceeds the maximal calcium influx throughout the voltage-gated L channels in the hippocampus. Although the bulk of Ca^{2+} influx evoked by glutamatergic stimulation reflects activation of the NMDA channels, the L channels and Na^{+}/Ca^{2+} exchange are secondarily involved in this phenomenon. Several calcium-related processes have been suggested to play the role of effector mechanisms cooperatively participating in the excitotoxic and ischemic neuronal injury. In this context the NMDA receptor-induced, Ca^{2+}- and phospholipase A_2-mediated arachidonic acid (AA) release deserves consideration. Recently involvement of AA in the mechanism of long term potentiation of glutamatergic fast excitatory neurotransmission in the hippocampus, and AA-evoked protein kinase C activation in the brain were shown. This suggests that AA and/or its metabolites may induce pathogenic amplification of cell signalling mechanisms in neurons, thus mediating their injury.

S4.7 SYNAPTOSOMAL TRANSPORT AND METABOLISM OF GLUTAMATE PRECURSORS IN HYPERAMMONEMIA.

J. Albrecht, L. Faff-Michalak, W. Hilgier and *U. Rafałowska,
Departments of Neuropathology and *Neurochemistry, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland.

Moderate hyperammonemia (HA) was induced in rats by 3 i.p. administrations at 24h intervals of a hepatotoxin - thioacetamide (model A), or ammonium acetate (model B). HA in model A inhibited the uptake to cerebral synaptosomes of glutamine, which is a major metabolic precursor of glutamate (GLU). Of the precursors playing a minor role, HA inhibited the uptake of ornithine, but stimulated that of 2-oxoglutarate (2-OG) and arginine (ARG). HA enhanced the synaptosomal activity of enzymes involved in ARG metabolism to GLU: arginase and ornithine aminotransferase. HA in models A and B, but also in vitro treatment with ammonium chloride, inhibited the malate-aspartate shuttle enzymes: malate dehydrogenase and aspartate aminotransferase, as well as the glutamate dehydrogenase activity in the direction 2-OG towards GLU, and the inhibitory effects involved the synaptic but not the nonsynaptic mitochondria. Pyruvate carboxylase, the astrocytic mitochondrial enzyme thought to furnish 2-OG for the synaptic synthesis of GLU, was markedly inhibited in the nonsynaptic mitochondrial fraction. The results taken together point to the decrease of the synaptic glutamate formation as a cause of failure of excitatory neurotransmission during HA.

Symposium (S5) - Neuromuscular disorders

S5.1 ACCUMULATION OF BETA-AMYLOID PROTEIN (bAP) AND ITS PRECURSOR (bAPP) IN VACUOAED MUSCLE FIBRES OF INCLUSION-BODY MYOSISTIS; SILILARITIES TO ALZHEIMER'S DISEASE BRAIN

V. Askanas, W. K. Engel, R.B. Alvarez, Los Angeles

Not received

VIRAL DISEASES OF NEUROMUSCULAR SYSTEM S5.2

L. P. Weiner, Los Angeles

Not received

S5.3 Molecular Mechanisms of Treatment of Dysimmune and Viral Neuromuscular Diseases.

W. King Engel
USC Neuromuscular Center, University of Southern California School of Medicine, Los Angeles, CA.

I. **ANTI-DYSIMMUNE.** A. Circulating Malantibody - **1. Stop antigenic stimulus:** a) remove antigen (e.g. virus, toxin or gene abnormality that "foreigned" the cell) b) hit presenting macrophages. **2. Stop antibody production:** i) Hit upregulated a) antibody-producing B-cells, b) T-helpers/their receptors, c) facilitating cytokines; ii) Help d) T-suppressors, e) inhibitory cytokines. **3. Address circulating malantibody:** a) remove, b) give anti-idiotype antibody. **4. Block action on target cell (e.g. with IVIG):** a) specific receptor (Fab), b) non-specific receptors (e.g. Fac). B. Cytotoxic T-cells - **1.** as A-1. **2. Stop mal-T-cell production:** a) Hit upregulated cytotoxic T-cells/their receptors. b-e) as in A2. **3. Address T-cell cytotoxic products:** a) block release, b) block receptor site. **4. Block action on target cell:** a) specific receptors, b) non-specific receptors. C. Mast cells/products - block proliferation, release of products. D. Drugs discussed include - prednisone, cyclophosphamide, 2-chlorodeoxyadenosine, cyclosporin, lazeroids, cromolyn, α-interferon, thalidomide, monoclonal antibodies, cytokines.

II. **ANTI-VIRAL 1. Attack the virus:** a) kill, b) stop proliferation (e.g. anti-reverse transcriptase). **2. Stop effect on infested cell:** at level of viral or cell a) DNA/RNA, b) protein **3. Stop effect on organism:** a) dysimmune reaction (e.g. in HTLV-1 myelopathy), b) others.

Possible consequence of disruptions of neuromuscular contact in early development S5.4

Professor Gerta Vrbová, Department of Anatomy and Developmental Biology, University College London.

Shortly after birth motoneurones and muscles are critically dependent upon continued contact with each other. If interaction between the 2 cell populations is temporarily disrupted motoneurones die, and muscle development is permanently impaired. The possible cause of motoneurone death in this situation will be discussed. Evidence will be presented to support the hypothesis that interaction with the target muscle is necessary for the motoneurones to become competent to survive the increase of afferent excitatory inputs that occurs during the development of the CNS. Strategies that could prevent or counteract motoneurone loss after target deprivation will be suggested.

The dependence of skeletal muscle fibres on continued contact with motoneurones persists even longer after birth. In rats at 5 - 6 days old motoneurones no longer require contact with the muscle for their survival, but muscle fibres still depend on motoneurones. At this stage muscle fibres have several inputs. With development this polyneuronal innervation gives way to the adult situation where each muscle fibre is contacted by only 1 axon. Evidence will be presented to show that the initial excessive input that is polyneuronal innervation is essential for normal muscle development.

S5.5 MECHANISM OF CLINICAL MANIFESTATION OF MOTOR UNIT DESINTEGRATION IN MOTOR NEURAL DISEASES

B. M. Gecht, Moscow

Not received

S5.6 **INTERRELATIONSHIP BETWEEN GENE, ITS PRODUCT AND PHENOTYPE IN DMD/BMD**

I. Hausmanowa-Petrusewicz, J. Zaremba, A. Fidziańska
J. Zimowski, B. Badurska, E. Fidziańska, A. Łusakowska,
J. Borkowska

Neuromuscular Unit Medical Research Center Pol.Ac.Sci;
Department of Genetics, Institute Psych. Neurol.;
Department of Neurology Medical Academy, Warsaw,Poland

Analysis of DNA was performed in 84 families affected with muscular dystrophy Duchenne type (DMD) or Becker type (BMD). Deletions were detected in 49 families (58 %). In the same families the test for dystrophin was carried out. In the analysis of material extent of deletion, amount of dystrophin and clinical status were considered of 10 cases of BMD deletions were detected in 9 cases, usually involving exons 45-52. A marked variability regarding the amount of dystrophin was involved in cases of BMD. Attention is drown to female case with DMD and X-autosomal translocation; one family with detected deletion and apparantely normal dystrophin; one family with abnormal dystrophin and deletion but close to normal level of CK.
The diagnostic importance of those findings is discussed.

Symposium (S6) - Sensory networks: anatomy, physiology, modelling

S6.1 SPECIFICITY OF NEURONAL CONNECTIONS IN THE VISUAL THALAMUS OF THE CAT

A. Wróbel[1], S. Lindström[2] and M. Bekisz[1].
[1]Nencki Institute, Warsaw, Poland and [2]University of Gothenburg, Sweden.

A typical principal cell (PC) of the dorsal lateral geniculate nucleus receive monosynaptic excitation from 1-3 retinal ganglion cells of one eye, the same center type (on or off) and belonging to either the X or Y system. It receives also the inhibitory connections from several feed-forward intrageniculate interneurones with the same specific pattern, and via recurrent perigeniculate neurons of corresponding X/Y categories, but binocular and of on/off type. The deviations from this typical connection scheme were checked intracellularly in a sample of 500 PCs. Four (0.8%) PCs received binocular, and one (0.2%) mixed excitation from on- and off-center ganglion cells; all five were Y neurons. Two percent of the X PCs received additional EPSPs from Y retinal fibers, while 20% of Y cells - small EPSPs from X fibers. The atypical excitation was quantitatively small and did not affect significantly the firing of the cells. With no exceptions the on- or off-center PCs were inhibited by type specific (on or off) feed-forward interneurones and only 1% of the X PCs received a small IPSP from Y pathway (no IPSPs originated from X pathway were found in Y PCs). In our experiments the recurrent inhibitory system was found to be also specific, although in the extracellularly recorded sample of 90 perigeniculate cells 14% had mixed X/Y input. The specificity of connections in the visual thalamus is striking. The rare atypical inputs seem not to change the output characteristic of the visual thalamic cells.

S6.2 **POSITIVE FEED-BACK CIRCUITS AND EPILEPTIC SEIZURE IN THE CAT'S VISUAL CORTEX**

**S. Lindström, A. Hedström, E. Taubol and A. Wróbel,
Department of Physiology,
University of Göteborg, Göteborg, Sweden.**

It is an old notion that focal epileptic seizure develop as an oscillation of neuronal activity in closed excitatory neuronal chains within the cortex and between the cortex and subcortical structures. We have identified several such chains in the early visual system of the cat. The role of different elements in these circuits for seizure initiation and maintenance will be reviewed together with examples of mechanisms of action of some antiepileptic drugs.

S6.3 **The organization of the visual system in primates: an evaluation of theories and the use of the comparative method**

Jon H. Kaas, Psychology Department Vanderbilt University Nashville, TN 37240

Over the last 20 years considerable progress has been made in understanding the organization of the visual system in primates. Current proposals from a number of laboratories portray visual cortex as an extensive sheet of tissue that is subdivided into as many as 20-30 visual areas, each connected with several others to form a complex processing array. While there are many features of agreement across proposals, there are also notable differences. Comparative studies across primate and even non-primate taxa can help resolve these differences. Since all mammals evolved from a common ancestor, all brains are modifications of a common plan, and can be understood, in principle, as modifications of the common plan along branching lines of descent. Therefore, any theory of organization proposed for any specific taxonomic group can be evaluated, not only by the evidence for that group, but also by the degree of compatibility with evidence from other taxa, especially sister groups. Such a comparative approach suggests that current proposals of visual cortex organization contain errors and misinterpretations. The differences in theories indicate regions of cortex of uncertain organization and of the need for further investigation.

S6.4 Neurochemical characterization of projections in the cat visual system. Leo M. Chalupa, Center for Neurobiology, University of California, Davis CA 95616 U.S.A.

The availability of antibodies directed at putative neurotransmitters and neuromodulators has made it feasible to relate the morphological and functional properties of selective populations of cells in the mammalian visual system to their neurochemical content Evidence will be provided that two major classes of cat retinal ganglion cells (alpha and gamma) can be differentiated on the basis of their content of different neuropeptides (somatostatin and neuropeptide Y, respectively). Interestingly, not all alpha cells are immunoreactive for somatostatin (SRIF). Rather, the SRIF-immunoreactive alpha cells are preferentially localized in the inferior retina. Collectively, the available immunohistochemical results indicate that the functional diversity of retinal ganglion cells in the mammalian visual system may be greater than suspected on the basis of previous anatomical and electrophysiological findings. (This work was supported by research grants from the National Institute of Health)

S6.5 DIFFERENT FORMS OF PLASTICITY IN THE BARREL CORTEX

MAŁGORZATA KOSSUT
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Besides changes in morphology of the barrels following neonatal destruction of vibrissal follicles (Van der Loos and Woolsey, 73), several manifestations of plasticity can be demonstrated in the barrel cortex. Changes of spatial pattern and intensity of functional activity can be found in the cortex after both neonatal and adult denervation of rows of barrels. Sensory deprivation without damage to nerve endings (by cutting off the whiskers) also alters functional activity of cortical vibrissal columns. Barrel cortex in the adult rat can be invaded by afferents from non-vibrissal receptors - after removal of vibrissae stimulation of the common fur of the mystacial pad can activate the barrel field. This last process takes much longer to develop than the intra-barrel field plasticity. Stimulation of a row of whiskers during a sensory conditioning training can increase the cortical representation of this row already after 30 min of stimulation. Different mechanisms are suggested for processes occurring within the barrel field and as a result of interactions of the barrel field and neighboring cortical regions.

S6.6 **Conversion of Temporal Correlations Between Stimuli to Spatial Correlations Between Attractors**

Daniel J. Amit, INFN, Sezione di Roma, Istituto di Fisica Universita di Roma, La Sapienza, Ple Aldo Moro, Roma
(On leave of absence from Racah Institute of Physics)

Single electrode recordings in performing monkeys by Miyashita et al, show that the internal representations of uncorrelated images memorized in associative cortex reproduce in their activity distribution the temporal correlations present in the training sequence. The internal representations exhibit correlations up to the fifth neighbor in the training sequence. These experiments are described in detail.

A simple modification of synaptic structures (of the Hopfield type) constructed to produce auto-associative attractors, produces neural networks whose attractors are correlated with several (learned) uncorrelated patterns used in the construction of the matrix. The modification stores in the matrix a fixed sequence of uncorrelated patterns, introducing couplings between patterns which are nearest neighbors in the sequence. The network then has correlated attractors, provoked by uncorrelated stimuli. The attractors are correlated up to the fifth neighbor. Thus, the network converts the temporal order (or temporal correlation) expressed by the sequence of patterns, into spatial correlations expressed in the distributions of neural activities in attractors. This number 5 is universal in a range of parameters, and requires essentially no tuning.

We then discuss learning scenarios which could lead to this synaptic structure as well as experimental predictions following from it. Finally, we speculate on the cognitive utility of such an arrangement, emphasizing in particular their potential role in priming effects.

Workshop (W4) - Excitatory amino acids: clinical aspects

W4.1

Parsons, C.G. and Quack G.
Merz + Co. GmbH & Co., Eckenheimer Landstraße 100-104, 6000 Frankfurt am Main 1, Germany.

MEMANTINE - SAFE AND THERAPEUTICALLY EFFECTIVE MODULATOR OF GLUTAMATE RECEPTORS.

Memantine was tested as an antagonist of N-methyl-D-aspartate (NMDA) receptors in cultured superior colliculus and hippocampus cells using the patch clamp technique in the whole cell mode. Memantine (2 to 16μM) selectively and concentration-dependently antagonized responses to NMDA 100μM with an IC_{50} of 2.58 ±0.16 μM. In contrast, current responses to (S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (L-AMPA) and gamma-aminobutyric acid (GABA) were unaffected by Memantine 8μM. Memantine 8 μM caused a non-parallel shift of the NMDA dose-response curve to the right indicative of a non- or uncompetitive mechanism of action. However, the antagonistic effects of Memantine were not reversed by increasing concentrations of glycine (1-100μM) ruling out the possibility of an interaction of Memantine with the strychnine-insensitive glycine site associated with the NMDA receptor-channel complex. Previous studies have demonstrated that nM concentrations of Memantine displace the binding of the prototypic NMDA channel blocker MK-801. As the effects of Memantine seen in this study were both use- and voltage dependent it seems likely that Memantine, like MK-801, exerts its antagonistic effects through an open channel block of the NMDA receptor/channel complex. However, the use-dependency of this uncompetitive antagonism showed much faster kinetics than reported by others for MK-801. Furthermore, unlike MK-801, Memantine actually potentiates synaptic transmission in the CA1 region of hippocampal slices. The precise mechanism of action for this effect is unclear but may be related a, to modulation of AMPA receptors following an increase in PI turnover, possibly via activation of metabotropic glutamate receptors and b, to the faster kinetics of the NMDA blockade. It therefore seems likely that many of the positive effects of Memantine seen in the treatment of dementia can be explained by its properties as a modulator of glutamatergic transmission.

W4.2

INTERACTION OF NMDA RECEPTOR ANTAGONISTS AND ANTIDEPRESSANT DRUGS

J. Maj, Cracow

Not received

W4.3

Excitatory amino acid antagonists and the therapy of epilepsy.

Astrid G. Chapman, Department of Neurology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF.

Excitatory amino acid antagonist acting at different sites of the NMDA recptor, as well as at the non-NMDA receptors, exhibit potent anticonvulsant activity in a number of animal seizure models. Thus, NMDA- and non-NMDA (e.g. NBQX or GYKI 52466) antagonists provide potent protection against reflex-induced seizures in rodents (sound-induced seizures in DBA/2 mice or GEPR rats) or primates (photically-induced seizures in Papio papio), against a range of chemically- or electrically induced seizures, or against development of seizures by kindling. Selective, competitive NMDA antagonists (eg D-CPPene, CGP 37849 or CGP 39551) provide prolonged anticonvulsant protection following their acute administration to rodents or primates, with more favorable therapeutic ratios observed than those seen for the non-competitive NMDA antagonists acting at the channel site (eg MK 801 or dextromethorphan). The anticonvulsant potencies of the competitive NMDA antagonists, AP7 or CPPene, do not appear to be dimished following their chronic administration. Most of the currently available strychnine-insensitive glycine antagonists acting at the NMDA receptor have poor CNS uptake and a short time-course of action. However, following their acute, icv administration this group of antagonists offer promising anticonvulsant protection in several animal seizure models.

W4.4

Therapeutic prospects of excitatory amino acid antagonists in neuronal degeneration.

Brian Meldrum, Department of Neurology, Institute of Psychiatry, London, SE5 8AF, U.K.

Excitotoxic mechanisms contribute to selective neuronal damage occurring after cerebral ischemia, cerebral and spinal trauma and status epilepticus. They may also contribute to cell loss in various chronic neurodegenerative disorders.
In animal models of focal ischemia NMDA antagonists (such as D-CPPene and dizocilpine) administered within 60-90 min of the occlusion decrease the volume of cortex showing infarction. Similar effects are also seen with the non-NMDA antagonists, NBQX and GYKI 52466. The latter compounds are also protective in models of transient complete global ischemia. Behavioural outcome is also improved in models of spinal or cerebral percussion injury. Limbic system pathology is reduced by NMDA antagonists given during status epilepticus.
Stroke and trauma appear the most promising immediate therapeutic targets for excitatory amino acid antagonists but the design and conduct of apropriate clinical trials remains a formidable task.

Workshop (W5) - Functional hemispheric asymmetry: neuropsychological and electrophysiological aspects

W5.1 **INTERHEMISPHERIC TRANSMISSION TIME AND FUNCTIONAL ASYMMETRY OF THE HUMAN BRAIN.**

NOWICKA A.*, FERSTEN E.**, GRABOWSKA A.*

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Several reaction time studies suggest that interhemispheric transfer of information plays an important role in the formation of functional brain asymmetry. One could hypothesize that, depending on which hemisphere is dominant for a given function, the transfer of information from one hemisphere to the other is not equally effective. The present study aimed at veryfying this hypothesis by an electrophysiological (VEPs) method. Specifically we tested whether the interhemispheric transmission time (ITT), (measured as a difference between latencies of VEPs registered in the hemisphere ipsilateral to the stimulated hemifield and those registered in the contralateral hemisphere) depends on the type of the processed material (verbal vs nonverbal). Twenty two right handed subjects participated in two experimental sessions. In one session VEPs were recorded in response to 12 different 3-letter words, randomly appearing in the left and right visual field for 20 ms. In the other session 12 square-wave laterally presented gratings of various spatial frequencies were used as stimuli. Electrodes were located over the left and right occipital lobes at O1 and O2 according to the 10/20 system and referenced to linked ear lobes. The latencies of three VEPs components (P100, N170, P300) in the left and right hemisphere were compared. As expected the latencies of VEPs registered in the hemisphere contralateral to the stimulated hemifield were shorter than the latencies of VEPs recorded in the ipsilateral hemisphere. This difference was evident in two earlier (P100 and N170) components for both types of material. ITT depended on the type of material: for words ITT was shorter when the information was transfered from the right hemisphere to the left one, while for gratings, it was shorter when the information was transfered in the opposite direction. The results support the view that interhemispheric transfer is an important factor influencing the functional brain lateralization.

W5.2 Generalization of Induced Interhemispheric Interference: A Chronometric Approach to One-brain Vs Two-brains Models of The Hemispheres' Cooperation

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A reaction time study with normal subjects was conducted to obtain some support for one or the other model of interhemispheric relations - referred to as the "one-system" and the "two-systems" hypotheses. 12 subjects were extensively trained in a complex reaction time task consisting of a "priming sub-task" which introduced interhemispheric interference and two different "test sub-tasks" measuring the generalization of interference.
The interference priming produced visible slowing of RT's on the following trials. Interestingly, the deterioration of the two test sub-tasks was alike, despite the marked difference in the amount of the interhemispheric communication they required. This result is more in line with the one-system hypothesis, as the two-systems hypothesis predicts deterioration proportional to the amount of the required interhemispheric communication.

W5.3 HEMISPHERIC DIFFERENCES IN NONVERBAL VISUAL MATERIAL PROCESSING.

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Research findings indicate a more consistent pattern of hemispheric asymmetry for the auditory rather than visual modality, and within the latter - for verbal rather than nonverbal material. The effect of nonverbal visual material codability (susceptibility to verbalization), on functional hemispheric asymmetry was studied using pairs of figures of either easy or difficult codability (as assessed by the author in his earlier research). Four groups of 20 healthy subjects each were run: of righthanders, male (RM) or female (RF), and lefthanders (LM,LF). No interhemispheric differences were obtained for easy figures, while for difficult material the right hemisphere superiority, i.e. shorter RTs was found, but only in righthanders of either sex. The results suggest that uncontrolled codability of nonverbal visual material may lead to discrepancies reported in the literature.

W5.4 CEREBRAL LATERALIZATION AND SEVERITY OF STUTTERING IN CHILDREN.

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This experiment was designed in order to test the effect of different severity of stuttering on hemispheric asymmetry in visual perception of verbal material.
We tested 9 severe stuttering, 11 mild stuttering and 48 fluent speakers aged 13-15 years. Severity of stuttering was assessed by Iowa 7-point scale. The subjects were asked to identify 3-letter words presented on the screen in the left or right visual field for 20 ms. The children answered by pointing to the exposed word on the response card. The number of errors showed that while the performance of the normal speakers was consistent with literature on hemispheric specialization, the asymmetry was reversed only in severe stuttering. In mild stuttering the pattern of asymmetry was similar to that found in normal speakers. Our results show the different cerebral lateralization and the engagement of the right hemisphere in processing verbal material only in severe stuttering children.

W5.5 Hemi-neglect in left- and right-brain-damaged patients

Anna Herzyk, Łucja Spiewla
Maria Curie-Skłodowska University

A great amount of clinical data confirms spatial deficits limited to one half of the space. It is still not determined if neglect symptoms form an isolated syndrome or they contribute to the global nonspecific spatial impairment after right-hemisphere lesions. The main question of the present study is: do the manifestations of neglect correlate with the lateralization of brain lesion. The following tasks were used to evoluate neglect: line crossing, line bisection, drawing, detail adding. The method of directed interview was used to assess anosognosia. The differences between right- and left-brain-damaged patients performance are analysed. Some methodological questions are discussed.

Functional hemispheric asymmetry: neuropsychological and electrophysiological aspects

W5.6 Title: Discourse functions and hemispheric assymmetry. Author: Emilia Osiejuk M.A. Faculty of Psychology, Unieversity of Warsaw.

This presentation will review the main results of an application of discourse analysis in aphasics with left hemisphere damages (LHD) and right hemisphere damaged patients (RHD). The cognitive processes connected with micro- and macrostructure of discourse will be defined. The differences and similarities of processing at these structures of discourse in LHD and RHD patients will be presented on the base of current researches. The results of experiment on knowledge of scripts and plans as the most cognitive representation connected with discourse will be also considered. Obtained data indicate that aphasics have marked deficits on the level of microstructure, especially cohesion of discourse, whereas the coherence and superstructure of their texts are relatively well preserved. RHD patients show difficulties at the microstructure of discourse but not so marked as in aphasic patients. The main impairments of RHD patients' discourse can be observed at the levels of text coherence and superstructure. The both populations have also preserved cognitive representation concerned with scripts and plans. Abilities to abstract thinking are affected in aphasics as well as in RHD patients. These results indicate that the correct processes in both hemispheres are necessary for normal discourse processes.
Workshop: Functional assymmetry: neuropsychological and electrophysiological aspects.

W5.7 THE SIGNIFICANCE OF STUDIES IN COGNITIVE BRAIN MECHANISMS FOR CULTURAL ANTHROPOLOGY

Jan Kordys
Institute for Literary Research, Polish Academy of Sciences

The research of neuropsychologists on cognitive brain mechanisms and certain models implied by it, have become indispensable for the analysis of human symbolic activity and its evolutionary development. This especially concerns the relation between language and signs of a different morphology, associated with different functional brain structures (e.g. icons, music, gestures). At the communication level, the emergence of human society is characterized by a combination of two processes. First, the development of symbolic systems, and second, their capacity for modelling interpersonal relations. A successful combination of these two processes enabled the transition from general cooperation mechanisms among non-related group members (Axelrod and Hamilton's model) to specifically human forms of cooperation. These transformations were accompanied by changes within the functional architecture of the cognitive apparatus and included the formation of a collective community memory, the symbolization of human forms of ownership and kinship, as well as the appearance of mythology and deities responsible for exchange, acceptance and treatment of aliens. Modular models form a sound theoretical basis for the description of such transformations.

W5.8 INDIVIDUAL DIFFERENCES IN RELATIVE HEMISPHERIC ALPHA ABUNDANCE AND REACTION TO PERSUASION

Marek Cielecki
University of Warsaw

Left (LH) and right (RH) hemisphere-specific mechanisms of reaction to persuasion were studied in 32 males. Each subject was presented with 4 attitude objects, of which 2 were unimportant and 2 important. Of each pair, 1 object was presented verbally and 1 visually. Following each presentation, the subject was exposed to a counterattitudinal message from a purported expert source. EEG was recorded from the left and right parietal areas, sampled 100 times/sec. and filtered through a 8-13 Hz band -pass filter, yielding a relative LH to RH activity alpha abundance index. Hemisphericity was assessed on the basis of mean EEG index from initial and final resting epochs. Changes in objects positivity and importance were measured on standard dimensional scales and with a manipulospatial task devised to tackle responses produced by RH activity. Subjects also listed and assessed evaluativeness of thoughts generated in the course of experiment. Results showed that (a) LH subjects yielded more than RH subjects; (b) LH subjects differentiated their responses more to objects presented verbally, whereas RH subjects - to those presented visually; (c) changes in positivity were pronounced more on dimensional measure whereas in importance - on manipulospatial measure;and (d) no support was found to the claim that RH mediates attitudinal changes through increased evaluativeness of thought. These results are discussed in terms of LH and RH specialization.

Workshop (W6) - Neuromuscular disorders

W6.1 PATHOLOGY OF MITOCHONDRIAL DISEASES. B.Lach, S.DiMauro, E.Shoubridge, H.J.Mount, F.J. Lee, B.Kosabek-Williams, D.Preston, V.DaSilva. Univ. Ottawa, Min. Health and Welfare, and Montreal Neurol Inst., Canada, and Columbia Univ. New York, USA.

Maternally inherited mitochondrial diseases are characterized by a multiplicity of neurological manifestations (ie. strokes, blindness, epilepsy, myoclonus and neuropathies), ragged red fibers (RRF) in muscle biopsies, and mitochondrial DNA (mDNA) abnormalities. Mothers are obligatory carries, fathers do not transmit, while male and female offspring may clinically express the disorder.

We carried-out histochemical, biochemical, morphological, tissue culture (TC) and mDNA studies of striated muscle and fibroblasts from muscle and skin biopsies of four families with Leber's Hereditary Optic Atrophy (LHOA, 7 patients, clincially affected and unaffected males and females), a family with myoclonus epilepsy with RRF and stroke-like syndrome (MERRF/MELAS, 3 females, with post-mortem studies), and one female with Leigh's Disease (LD, biopsies and post mortem tissues).

Electron microscopy showed accumulation of mitochondria (M) in striated muscles in biopsy specimens and in many cells of epithelial, and mesanchymal origin. Ultrastructural M abnormalities persisted in TC. Moreover, in LHOA, M abnormalities were present in subclinical female carriers as well as in the affected individuals. In post-mortem material of LD and MELAS/MERRF patients, widespread distribution of M abnormal in the tissues, did not correlate with clinical phenotypes of the diseases. However, the common change to all these disorders was accumulation of M in smooth muscles and pericytes of capillaries, thickening and reduplication of vascular basal lamina, and necrosis of pericytes. Microangiopathy correlated better than presence of abnormal M or the type of heterogeneous mDNA abnormalities, with the onset and/or clinical expression of the diseases.

Our studies support the concept of MELAS/MERRF syndromes and LHOA as a systemic mitochondrial diseases. Moreover they point to crucial role of angiopathy in the clinical expressions of these disorders.

W6.2 **MUSCLE STIFFNESS AND CONTINUOUS ELECTROMYOGRAPHIC ACTIVITY IN OLD RATS; AN ANIMAL MODEL OF SPASTICITY?**

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A mechanomyographic response of the hind foot to passive straightening and bending, as well as an electromyographic activity of the gastrocnemius and tibialis anterior muscles were recorded in old (35-44 month-old) and young female rats. In old rats spontaneous, tonic electromyographic activity patterns were concurently observed in both antagonistic muscles; they were a low-amplitude, dense tonic activity and a continuous, high-amplitude, sparse electromyographic activity. The tonic electromyographic activity was correlated with a decline in the strength and mass of muscles, as well with motor disturbances, including paresis of the rigidly straigthened backward hind legs, dragged behind by an animal. In muscles of the old rats morphological features of a chronic denervation atrophy were found. Baclofen (10 and 15 mg/kg ip) diminished the spontaneous tonic electromyographic activity and potently decreased the whole body muscle tone, whereas Madopar (50 mg/kg of l-DOPA + 12.5 mg/kg of benserazide) was ineffective.

It is suggested that old rats in which the above-described pathologic alterations are observed might be a useful animal model in search for basic etiopathological mechanisms of spasticity and similar disturbances found in humans.

W6.3 **MU FIRING CHARACTERISTICS IN HUMAN DYSTROPHIC MUSCLE**

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During isometric contractions of constant force surface EMG as well as intramuscular MU potentials from extensor digitorum communis and biceps brachii muscles were recorded on magnetic tape for further off-line analysis. Surface EMG power spectra were computed and transformed so as to reveal low-frequency peaks which might correspond to MU firing rates. From intramuscular recordings, single MU action potentials were identified with an aid of semi-automatic recognition program. For each single MU action potential train (MUAPT) statistical parameters of interspike intervals (ISIs) such as mean value, standard deviation, skewness, curtosis and serial correlation coefficient were determined and related to the measured muscle force level. 64 MUAPTs from 8 patients and 55 MUAPTs from 3 normals were analysed so far.

The low-frequency part of surface EMG power spectrum from dystrophic muscle contains much more rate-related peaks than that from normal muscle. This means probably that in diseased muscle the MU firing rates are more widely dispersed.

From the parameters of MUAPTs, only firing rates and standard deviations of ISIs have shown significant differences between normal and dystrophic muscle. The MU firing rates were higher in muscular dystrophy and this difference was more pronounced for higher levels of muscle force. The tendency towards mean MU firing rate increase is stronger for the patients with more advanced disease.

The typical dependency of standard deviation of ISIs on their mean value may be approximated by two lines of different slope. There were reported experimental data indicating that the breaking point of this dependency may be an estimate of AHP duration in motoneurones. Our results for dystrophic muscle showed a shift of this breaking point towards shorter ISIs, as compared to normals. This suggests that in muscular dystrophy also motoneurones may be altered, either by the disease itself or as a compensation for changes in muscular part of a MU.

W6.4 **COMPLEX AND REPETITIVE MOTOR UNIT POTENTIALS IN MYOGENIC AND NEUROGENIC MUSCLE DISEASE**

Katarzyna Rowińska-Marcińska

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The study was undertaken to evaluate the complexity of motor unit potentials (MUP) as an index of desintegration of motor unit (MU) in progressing primary and neurogenic muscle diseases.
Material comprises 231 electromyograms (emg) performed in 84 patients (25 ALS cases, 29 SMA cases, 30 DMD cases) and 20 healthy volonteers. During the coherent CN EMG study the MUP with satellite components and double discharging MU were revieved.
The 529 complex MUP and 64 double discharging MU were found.
The amplitude and duration of individual components were measured.
Results were correlated with clinical data (duration of the disease muscle force and wasting).
Diagnostic yield of complex MUPs and double discharging MU prevelance in neuromuscular diseases is discussed.