Unawareness of deficits and emotional dysfunction after right-hemisphere insult: case studies

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Emotional changes appear to be a frequent consequence of brain injury. It is difficult to differentiate between emotional adjustment reactions and emotional symptoms of brain injury. Some findings suggest that patients' awareness of their own cognitive deficits is associated with increased risk for emotional dysfunction.

Cases of two patients with right-hemisphere lesions of vascular etiology and left hemiparesis are presented. The patients at about 16 and 32 weeks postinjury manifested unilateral neglect and low level of learning/memory abilities. The patients estimated their cognitive deficits and difficulties in every day life activities. The patients were also assessed with (1) observation, (2) interview and (3) questionnaires (Neuropsychology Behavior and Affect Profile, State-Trait Anxiety Inventory) in order to extract a kind of emotional profile. The relation between the insight about the level of cognitive impairments and emotional dysfunction (such as anxiety and depression) is discussed.

NEUROPSYCHOLOGICAL IMPAIRMENT IN WILSON'S DISEASE.

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We report the results of neuropsychological assessment of 50 patients with neurologic form of Wilson's disease (WD), 17 asymptomatic WD patients, 37 subjects with rheumatoid arthritis (RA) and 50 healthy controls. In conclusions, neurologically symptomatic WD patients, as compared to both asymptomatic WD patients and normal controls, showed cognitive impairment. They had relatively the poorest performance in task requiring attention, memory, learning, abstract thinking, as well visuo-spatial and conctructional skills. Although the hypothesis about impairment of some cognitive functions in symptomatic WD patients was confirmed, the degree of this deficit in treated persons turned out to be mild. No significant impairment of cognitive functioning and psychological well being was found in asymptomatic WD patients. In neurologically symptomatic WD patients, even if some affective or personality disorders are present objectively, they are not reflected in subjectively experienced and self-reported distress and psychological disability. Despite what was expected, no significant differences were noted between symptomatic WD patients, subjects with RA and normal controls in the self-report inventory measuring psychopathological symptoms.

Symposium 7 - Neuropsychology of cognitive functions

EVOKED CARDIAC RESPONSE AS A CORRELATE OF COGNITIVE PROCESSING IN THE CASES OF CENTRAL MOTOR SYSTEM IMPAIRMENT.

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We investigated the influence of motor neurons disease (Amyotrophic Lateral Sclerosis) on the Evoked Cardiac Response (ECR) elicited by auditory stimuli. The ECR is regarded as a specific physiological correlate of basic cognitive processes (stimulus intake, cognitive load). Stimuli were presented in two conditions defined by instruction allowing subjects to ignore the stimuli (IRRELEVANT condition) or requiring them to count silently the stimuli (RELEVANT condition). The main effect of instruction was obtained in the control group . The initial heart rate deceleration in the IRRELEVANT condition was significantly larger and a later acceleration in the RELEVANT condition was significantly larger. We did not found no significant difference between ALS group and control group in ECR obtained in IRRELEVANT condition, in contrast to RELEVANT condition. The ALS patients showed lack of accelerative component of ECR in RELEVANT condition, but similarly to subjects from control group they performed correctly mental task. The result is discussed in terms of role of primary motor cortex in evoking the accelerative phase of ECR in RELEVANT condition. Additionally, we compared this results to data obtained from the group of patients with another local impairment of cortical and subcortical structures.

SEX RELATED EFFECT OF UNILATERAL BRAIN LESIONS ON MUELLER-LYER ILLUSION.

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The relationship between gender and cerebral asymmetry has been extensively studied during past years but the picture emerging from those studies is still unclear. The inconsistencies specially concern the non-verbal visuospatial functions. The aim of this study was to investigate the effect of unilateral brain lesions on Mueller-Lyer (M-L) illusion.

Twenty five patients with left hemisphere (LH) damage (10 males and 15 females), 22 patients with left hemisphere (LH) damage (10 males and 12 females) and 23 control subjects (10 males and 13 females) participated in the experiment. They inspected series of 8 M-L patterns constructed in such a way that a distortion opposite to the original illusory effect was introduced to each configuration. The amount of this distortion increased in steps so that - at a certain point - the stimuli in a series started to produce a percept opposite to the original illusory one. Each version of M-L pattern was presented 5 times, in a random order. The subjects' task was to decide whether the shaft with out-going wings was longer than the shaft with in-going wings. The subjects' judgements were collected using a forced choice procedure. The number of judgements of two categories (longer-shorter) was calculated and the strength of illusion was established using the Spearman distribution method. Results showed sex related hemispheric asymmetry in subjects' susceptibility to the M-L illusion. The LH and RH lesions in females and RH lesions in males resulted in strengthening of the illusory percept, while LH lesions in males did not affect the illusion. Moreover, both controls and males with the LH lesion were able to correct partially their false percepts after several minutes of pattern inspection. The two groups of females with brain damage and males with the RH damage showed a deficit in that learning effect.

Our results support the view that the organization of visuospatial processing in the two hemispheres is different in males and females.

PARALLEL PROCESSING OF AUDITORY INFORMATION: NEUROPSYCHOLOGICAL AND ANATOMICAL EVIDENCE

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Several lines of evidence indicate that parallel processing is a major feature of the visual system. Strong support comes from reports of associative and apperceptive forms of visual agnosia and from evidence of multiple visual cortical areas. We have been searching for similar evidence in the auditory system.

Recognition of objects is possible from auditory information alone. We have studied different aptitudes putatively involved in sound object recognition in normal subjects and in brain-damaged patients: i) capacity to segregate sound object on different cues (intensity steps, coherent temporal modulation or signal onset synchrony); ii) asemantic recognition of sounds of real objects by judging whether two acoustically different sound samples belonged to the same objects; and iii) semantic identification of sounds of real objects. Sixty normal subjects provided normative data. Twenty brain-damaged patients were tested; in 12, different aptitudes involved in auditory recognition were disrupted separately and in a way which speaks in favour of parallel rather than hierarchical processing. We found no strong association between any deficits in non-verbal auditory recognition and aphasia or side of lesion.

Human auditory cortex found to respond to auditory stimuli comprises the supratemporal plane, the posterior part of the superior temporal gyrus and parts of insula. We have studied the pattern of cytochrome oxidase and acetylcholinesterase activity in 10 normal human hemispheres. Five dark and 3 light cytochrome oxidase regions were found in the auditorily responsive cortex; several of these areas correspondeded to distinct cytoarchitectonic subdivisions and had a particular acetylcholinesterase pattern as well. The identified areas corresponded to the primary auditory area and to 7 other putatively auditory areas.

Temporal constraints of cognition studied with the subjective rhythmization paradigm

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It has been well documented that the ability of the nervous system to integrate successive events is limited up to intervals of app. 3 sec. Recent studies have provided direct support for a relationship between temporal information processing (TIP) and speech which seems also to be temporally segmented in this time domain. In a series of experiments we tested whether the left hemisphere is non-specifically involved in this TIP (Exp.1), or the classical language areas in this hemisphere are selectively associated with temporal mechanisms (Exp.2). Further question was whether the measured integration interval length (MIIL) may alter across the life span (Exp.3,4). We tested 5 patient groups with acquired focal lesions (Exp.2), or healthy volunteers aged from 9 to 66 years (Exp.1,3,4). Subjects grouped beats generated by a metronome with different frequencies and presented either dichotically (Exp.1), or binaurally (Exp.2,3,4). The task was to accentuate mentally every 2, 3 ...etc. beat, to create a subjective rhythm. Subjects reported verbally how many beats they were able to integrate into a perceptual unit and MIIL (number of reported beats times the time distance between two successive beats for a particular frequency) was analyzed. The results indicate the lack of hemispheric asymmetry in MIIL (Exp.1). Specific TIP disorders were found depending on the lesion location (Exp. 2). In Broca's aphasia, MIIL was longer, especially for lower frequencies of beats, than in other participants, suggesting slowing down of their processing. We postulate, thus, timing disorders in Broca's aphasia which probably underlay language deficits characteristic for this aphasia syndrome. Moreover, MIIL depended on the frequency of presented beats (the higher frequency, the shorter MIIL). Although this relationship generally does not change across the life span (Exp.3,4), the normal chronological aging was associated with elevations of MIIL. To conclude, MIIL is not a stable feature, but varies across the life span depending on the mental content of the information processed. Broca's area seems to be particularly involved in this TIP.

PROVERB PROCESSING IN APHASICS AND NORMAL ADULTS

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The main questions concerned cognitive and linguistic strategies used by Ss and importance of Ss personal features (age, gender, education), proverb characteristics (familiarity, degree of abstraction), and task format (free response, multiple choice).

Task categories were connected with recognition, comprehension, and production.

Sixty normal adults and ten aphasics participated in pilot studies, twenty aphasics and twenty normals - in experimental ones.

Results: Proverb processing is preserved in aphasia, but linguistic deficits hinder verbalization of nonliteral meanings for proverbs (particularly unfamiliar ones).

There are differences in strategies used in normal controls and aphasics according to proverb features and task format.

There is continuum of errors among controls of different education levels and aphasics.

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LANGUAGE NEUROPSYCHOLOGICAL TESTS AND SPECT MEASUREMENTS IN ELDERS WITH MILD NEUROCOGNITIVE DISORDER

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Systematic examination of the functional changes occurring in elderly patients with mental deterioration has resulted in a neuropsychological assessment measure termed MODA (Milan Overall Dementia Assessment). MODA allows specific evaluation and is a useful tool as a screening test, but it does not allow selective correlation either with left- or right-cerebral hemispheric function. In the present study, a group of subjects, affected by Mild Neurocognitive Disease (MND), according to DSM IV and MODA, was thus further investigated with specific right-hemisphere and left-hemisphere language tests. In particular left-hemisphere neuropsychological test was the verbal dichotic listening (DL) test, while the right-hemisphere test was the test battery for evaluation of right hemisphere language capabilities (RHLC) by Bryan (1988 - in the standardized Italian translation by one of the Authors -S.Z.). Furthermore, clinical trials have outlined the contribution of advanced biomedical methods, i.e. SPECT (Single Photon Emitting Computerized Tomography) to map the topography of brain dysfunction. SPECT is less expensive and technically easier than PET scan and has the potential of being available as a screening diagnostic instrument in the clinical setting. In light of the foregoing information, it was considered of interest to assess, in hospitalized geriatric patients with MND, the reliability of MODA, DL and RHLC testing, together with information by functional neuroimaging (SPECT) to contribute to a clearer distinction between normal aging and early dementia. The contribution of SPECT as well as the neuropsychological testing to early diagnosis and early treatment of Mild Neurocognitive Disorder are discussed.

Symposium 8 - Mystery of basal ganglia

PARKINSONIAN-LIKE AND SENILE MUSCLE RIGIDITY

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Parkinson's disease appears predominantly in the aged, but similar motor disorders, e.g. muscle stiffness, are also seen in the course of uncomplicated ageing. Resistance to passive movements of the hind leg (MMG) of the rat and an electromyogram (EMG) of the flexor (m. tibialis anterior) and extensor (m. gastrocnemius) muscles of its leg were recorded simultaneously as a measure of the muscle tone. The increased muscle tone after reserpine (10 mg/kg ip), haloperidol (0.5-10 mg/kg ip) or 6-hydroxydopamine (6-OHDA) nigral lesions was accepted as a model of the parkinsonian-like muscle rigidity. Both reserpine and haloperidol potently increased the rat's muscle tone and the long-loop reflex EMG responses. That effect mimicked the muscle rigidity observed in the course of Parkinson's disease and that induced by neuroleptics in humans. The effects of 6-OHDA lesion of 70% (63-80%) of nigral dopamine cells (stained for tyrosine hydroxylase) were negligible whereas lesion of 89% (81-96%) of nigral cells produced a similar MMG/EMG muscle rigidity as did haloperidol or reserpine; that effect appeared, however, only 2 weeks after the lesion and disappeared already after 4 weeks. The results obtained with very old rats suggest that the muscle stiffness seen in old animals (predominantly in their flexors) is not due to a reflex response (which was blocked by lignocaine injected in the vicinity of the sciatic nerve), but depends mainly on non-reflex factors - mainly on a large overgrowth of the non-elastic connective tissue (reflected by an increased fibronectin content) within the muscles. These results suggest that mechanisms generating phenomenologically similar symptoms in parkinsonian patients and in the aged are different.

GLUTAMATERGIC INTERACTIONS AND STRATEGY FOR PHARMACO-THERAPY OF PARKINSON´S DISEASE

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The conventional dopaminergic strategy for the treatment of Parkinson´s disease is only partially satisfactory and, therefore, improved therapies are needed. Recent interest has focused on the use of glutamatergic N methyl-D-aspargic (NMDA) receptor antagonists. These compounds are able to facilitate dopaminergic function as evidenced by increased dopamine release and turnover in the striatum and reduced cataleptogenic effects of dopamine D-2 receptor antagonists. Furthemore, NMDA receptor antagonists may reduce methamphetamine and MPTP-induced neurotoxicity to the nigrostriatal dopamine pathway.

The detailed mechanism by which NMDA receptor antagonists produce antiparkinsonian effects in animal models is only partially elucidated. The critical mechanism is supposedly associated with blockade of the abnormally increased activity of glutamaterigic output from the subthalamic nucleus to other areas such as medial globus pallidus and substantia nigra pars reticulata. The GABA-ergic neurons located in these areas are able to reduce the function of thalamic nuclei and the resultant decreased thalamocortical activity is suggested to account for parkinsonian signs.

In addition, NMDA receptor antagonists produce anxiolytic effects due to influencing the function of the brain limbic areas such as nucleus accumbens and hippocampus.

EVENT-RELATED POTENTIALS IN BASAL GANGLIA DISORDERS

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Event-related potentials (ERP) have been widely employed in the study of human cognitive functions as methods allowing to analyse neurophysiological events underlying or paralleling mechanisms of information processing. Moreover, ERP were shown to reflect a mental slowing down associated with ageing as well as cognitive deficits in various disorders, e.g. in degenerative dementias, Parkinson's disease, metabolic encephalopathies, etc.

Movement disorders include various pathologies affecting the basal ganglia and their connections. Cognition is often impaired but characteristic motor disorder may interfere with common neuropsychological testing. The ERP's contribution to the clinical evaluation of cognitive deficits in movement disorders is still a moot point. The results are seldom specific enough and the differences between patients and normal controls are not big enough to be of individual diagnostic use. Most studies tend to make use of simple tasks of mono-modality discrimination ('odd-ball' paradigm), and interest is generally focused solely on P3 (P300) wave latency while important parameters (e.g. amplitude and scalp topography of ERP) tend to be overlooked. On the other hand, even under the simplest conditions, "subcortical" and "cortical" dementia can be differentiated on the basis of the ERP activity. More information could be obtained using paradigms that test the specific cognitive deficits and if more aspects of the ERP were quantified. In combination with other tests of mental function, ERP can be useful in continuous monitoring of the patients' status or of drug effects. Moreover, as movement disorders provide unique models of focal neurotransmitter deficits, ERP might serve better understanding of functional mechanisms at the basal ganglia and subcortico-cortical levels.

Dopamine induced programmed cell death (apoptosis) in postmitotic neurons - Implications for the pathogenesis of Parkinson's disease

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In Parkinson's disease, the major pathogenic substrate is death of the dopaminergic neurons in the substantia nigra. Cause of nigral degeneration is unknown, but is currently believed that excessive local oxidative stress is etiologically important. Mode of neuronal death in the parkinsonian nigra is also underdetermined. It was hypothesized that toxic free radical species cause lipid peroxidation, membranal disruption and neuronal destruction by necrosis. However, the slow and protracted nigral neuronal degeneration with absence of local inflammation suggests that the progressive death may be due rather to apoptosis. Dopamine, the natural neurotransmitter within nigrostriatal neurons, is an extremely toxic substance. We have shown that exposure to dopamine of postmitotic eg, chick sympathetic and rodent cerebellar and cortical neurons, and non-neuronal cells eg, PC12 and splenocytes, causes all the characteristic histochemical, molecular biological and scanning electron microscopical features of apoptosis. Dopamine-induced apoptosis could be prevented by co-treatment with thiol-containing anti-oxidants such as gluthatione and N-acetylcystein, suggesting that toxicity of dopamine is mediated by its free radical metabolic byproducts generated during its auto-oxidation. In addition, programmed cell death was prevented by inducing cellular overexpression of the anti-apoptotic protooncogene bcl-2. Using the differential display technique, we found that when postmitotic neurons are exposed to dopamine, they show two waves of massive induction of several cell cycle regulators eg., cyclin B and PCNA, before they go on and die by apoptosis. It is possible that the unsynchronized and simultaneous activation of cell cycle check points by dopamine is one of the major mechanisms in the cell suicide. We also found that exposure to dopamine induces a massive elevation of collapsin, a member of the semaphorine family of proteins. Latter belongs to a large group of axon guidance molecules that control and direct axonal path finding during brain development. Collapsin is a repulsive-destructive agent and works to destroy axonal growth cones that go astray and grow away from their planned target. We suggest that inappropriate action of dopamine, combined with additional yet unknown factors, may participate in the etiology of progressive nigral death in PD. Hypothetically, in the postmitotic, fully differentiated nigral neurons, dopamine (or other sources of oxidant stress) may inadvertently reactivate dormant and long-forgotten processes that are operational only in the developing brain including apoptosis, mitosis and axonal growth and target finding. Such activations may be incompatible with continued cell survival, and since the neurons cannot cope with these chaotic events, suicidal apoptosis programs are triggered leading to their death.

Surgical treatment of Parkinson's disease as a tool for an understanding of the basal ganglia function

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Stereotactic surgical treatment of Parkinson's disease is known for more than half a century. The exact mechanism by which inactivation of various structures by destruction or stimulation alleviates some of the symptoms is not clearly understood. The targets for stereotactic surgery changed over the years sometimes as a result of a better understanding of the role of these structures, sometimes by simple chance.

Surgical approach to Parkinson's disease includes: 1/ stereotactic destruction of various nuclei of thalamus, external and internal part of globus pallidus, and subthalamic nucleus, 2/ electrical stimulation of subthalamic nucleus, 3/ replacement of the deficient substantia nigra by transplantation of fetal mesencephalon. The suggested mechanisms of these procedures as well as their effectiveness will be presented.

Symposium 9 - Seizure phenomena and excitatory amino acid receptors

ANTICONVULSANT ACTION OF EXCITATORY AMINO ACID ANTAGONISTS IN DEVELOPING RATS

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Antagonists of excitatory amino acids (EAA) exhibit marked anticonvulsant action in various models of epileptic seizures in adult animals. Because of marked changes in sensitivity to EAA during brain maturation we started to study anticonvulsant action of EAA antagonists in immature rats. Generalized tonic-clonic seizures induced by pentylenetetrazol were suppressed by both competitive and noncompetitive NMDA antagonists (2-APH, CGP 37551, CGP 40116, ketamine, dizocilpine) at all stages of maturation studied with higher efficacy in youngest animals. On the contrary, nonNMDA antagonists (CNQX, DNQX, NBQX) exhibited only moderate action against these seizures. Epileptic afterdischarges elicited by electrical stimulation of sensorimotor cortical area could be reliably suppressed by nonNMDA antagonists (NBQX, GYKI 52466) throughout development. Action of NMDA antagonists (2-APH, CGP 40116, ketamine, dizocilpine) against this type of seizures was strong in most age groups studied but some developmental changes were observed. Both ketamine and dizocilpine powerfully suppressed afterdischarges in 12- and 25-day-old rats whereas their action in 18-day-old rat was only moderate and developmental profile of NMDA antagonists was even more complex. Unfortunately, EAA antagonists compromised motor performance in rat pups and, in addition, noncompetitive NMDA antagonists influenced behavior of the animals.

SEIZURE-RELATED ALTERATIONS IN THE EXPRESSION OF GENES CODING FOR EXCITATORY AMINO ACID RECEPTORS.

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Changes in the excitatory amino acid (EAA) receptor biosynthesis may be of vital importance to the regulation and/or adaptive response to seizures. To this end we studied alterations in the expression of NMDA and AMPA selective glutamate receptor genes in the rat hippocampal formation in various experimental models of limbic seizures, e.g. those evoked by systemic pilocarpine, kainate or pentylenetetrazole-induced kindling. As shown by an in situ hybridization study, all the convulsants studied evoked a decrease in the NMDAR1 and GluR2 flip mRNA levels in the CA1 and CA3 fields of the hippocampus; however those changes were differently time-dependent. In the dentate gyrus, the pilocarpine and pentylenetetrazole kindling raised the GluR2 flop mRNA level and lowered the flip one, whereas kainate evoked opposite effects. The above data indicate that seizures decrease the NMDAR1 mRNA level and differentially regulate the expression of flip and flop forms of GluR2. These effects may be a compensatory response to an oversupply of endogenous agonists during seizures, and may influence the efficiency of synaptic transmission in the epileptic hippocampal formation.

A FUNCTIONAL ROLE FOR NMDA RECEPTORS IN THE CONTROL OF COCAINE-INDUCED CONVULSIONS

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Convulsions associated with cocaine abuse can be life-threatening and resistant to treatment. In some models of cocaine seizures, even high, incapacitating doses of anticonvulsant drug standards are ineffective against cocaine convulsions. In contrast, functional antagonists of glutamatergic transmission protect against the toxic consequences of cocaine overdose. NMDA receptor antagonists dose-dependently prevent the clonic convulsions induced by cocaine in rodent models. The role of NMDA receptors in the control of cocaine-induced convulsive activity is strengthened by the finding that anticonvulsant activity can be achieved by blockade of both competitive and uncompetitive modulatory sites on the NMDA receptor complex. Thus, competitive antagonists, ion-channel blockers, polyamine antagonists, and functional blockers of the strychnine-insensitive glycine modulatory site of the NMDA receptor complex all prevent cocaine seizures. Although some NMDA blockers produce profound side-effects, significantly reducing therapeutic indices, others (e.g., low-affinity channel blockers, glycine antagonists) demonstrate significant separation in their anticonvulsant and side-effect profiles. The anticonvulsant efficacy of these compounds can be augmented by diazepam suggesting the potential clinical utility of such drug combinations. Interestingly, functional NMDA antagonists may also be of value in the treatment of cocaine dependence.

PHARMACOLOGICAL ACTIONS OF POSITIVE AND NEGATIVE MODULATORS OF AMPA RECEPTORS, IN VIVO AND IN VITRO

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2,3-benzodiazepines, such as GYKI 52466 or GYKI 53784, represent a new class of neurotropic agents with anticonvulsant, muscle relaxant, and neuroprotective properties. They exert their pharmacological actions through an allosteric modulatory site at the AMPA receptor. Cyclothiazide (CYZ), aniracetam (ANI), 1-(1,3-benzodioxol-5-ylcarbonyl)-piperidine (1-BCP), and another benzoyl-piperidine compound, BDP-12 are referred to as positive AMPA receptor modulators, as they enhance AMPA gated ionic currents by inhibiting the desensitization of the receptor.

GYKI 52466 and 53784 inhibited AMPA or kainate evoked spreading depression in isolated chicken retina. On the contrary, positive modulators, except for BDP-12, shortened the latency of spreading depression. CYZ, 1-BCP, and ANI potentiated AMPA-induced whole-cell currents, in acutely isolated cerebellar Purkinje cells, while BDP-12, again, was ineffective. On the contrary, BDP-12 enhanced AMPA responses when it was tested in cultured hippocampal neurons. 2,3-benzodiazepines inhibited AMPA or kainate currents, and the IC50 of GYKI 53784 did not change in the presence of 500 μM ANI. Similarly, negative modulators inhibited, while positive modulators enhanced synaptic field potentials in CA1 of hippocampal slices, and epileptic discharges were evoked in the presence of the latter ones. A great number of 2,3-benzodiazepine AMPA antagonists were found to be anticonvulsant in vivo, in the electroshock test and various chemically-induced seizure models. The positive modulator 1-BCP was found to be convulsive in urethan anesthetized rats and chloralose anesthetized cats. In the cat flexor reflex model, negative modulators blocked responses dose-dependently, while the positive modulator 1-BCP potentiated them.

Although the two classes of compounds had opposite effects in these experimental models, the results of most interaction studies suggested no competitive interaction between positive and negative AMPA receptor modulators.

NEUROACTIVE STEROIDS AS A TREATMENT FOR EPILEPSY. CURRENT STATUS AND FUTURE DIRECTIONS

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Epilepsy continues to be a significant clinical problem as current medications neither adequately control seizures nor are free of untoward side-effects. Neuroactive steroids (NAS) constitute a potential new direction for pharmaceutical interventions in epilepsy. NAS are devoid of genomic action; rather, they bind to a site on the $GABA_A$ receptor complex distinct from the binding site for benzodiazepines and barbiturates and thereby potentiate GABA-induced Cl^- influx. Additionally, some of NAS have been shown to attenuate glutamatergic neurotransmission and to block voltage-operated Ca^{2+} channels. NAS can be of endogenous or exogenous (synthetic) origin. Although endogenous NAS show a broad spectrum of the anticonvulsant activity against a number of animal models of epilepsy, their clinical utility is considerably limited by rapid biotransformation. Therefore, synthetic derivatives of naturally occurring NAS, ganaxolone and Co 2-1068, have been recently developed by CoCensys Inc. Experimental data obtained to date have defined the anticonvulsive profile of ganaxolone and Co 2-1068 and suggest their potential use in mono- and polytherapy of epilepsy. Importantly, the unique behavioral action of ganaxolone (see also *Beekman and co-workers* at the poster session) in the model of pentylenetetrazole-induced anxiety in mice suggests its potential in attenuating epilepsy-related psychiatric disorders. This presentation will summarize available data on the newly developed NAS in comparison with that of their parent drugs and conventional antiepileptic drugs against acute and chronic models of human epilepsy.

EXCITATORY AMINO ACID NEUROTRANSMISSION AND THE ANTICONVULSIVE ACTIVITY OF ANTIEPILEPTIC DRUGS

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Excitatory amino acids (EAA) produce convulsions when applied systemically or directly to the mammalian cortex. It was also documented that some cases of human epilepsy were associated with a significant increase in plasma EAA. Antagonists of both, N-methyl-D-aspartate (NMDA) and non-NMDA receptors, possess anticonvulsive activity in many experimental models of epilepsy. Although in many cases, antagonists of EAA potentiated the protective action of conventional antiepileptic drugs against maximal electroshock-induced seizures, some combinations (especially with NMDA receptor antagonists) resulted in severe adverse effects (Urbańska et al., Neuropharmacology 31,1021,1992; Żarnowski et al., Neuropharmacology 33,619,1994). Usually, non-NMDA receptor antagonists enhanced the anticonvulsive activity of antiepileptic drugs without accompanying undesired actions (Żarnowski et al., Neuropharmacology 32,895,1993; Borowicz et al., Eur. J. Pharmacol., 281,319,1995). Recent studies with the partial agonist at the strychnine insensitive glycine modulatory site within the NMDA receptor complex, D-cycloserine, and its combinations with carbamazepine or diphenylhydantoin are also promising (Wlaź et al., Epilepsia 37,610,1996). It is noteworthy that in no case of a combined treatment of an EAA receptor antagonist with an antiepileptic, a pharmacokinetic interaction could account for the observed potentiation of the anticonvulsive action.

Considering that 20-25% of epileptic patients do not respond to currently available medications (Sander, Epilepsia 34,1007,1993), a new approach for the treatment of epilepsy may be postulated. It is possible that the combined treatment of some EAA antagonists with antiepileptic drugs can provide a better protection and less adverse effects when an individual treatment.