The Effects of Unilateral Dopaminergic Deafferentation on the Expression of mRNAs of Neurotrophic Factors
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Recently protective and supportive functions of neurotrophic factors on dopaminergic neurons have been reported. In this study, in situ hybridization histochemistry with 32P-labeled oligonucleotide probes for brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) mRNAs was performed to determine the effect of unilateral deafferentation of midbrain dopaminergic cells with 6-hydroxydopamine (6-OHDA) on the expression of mRNAs of the above neurotrophic factors in the hippocampal areas. The deafferentation of midbrain dopaminergic cells induced changes of expression of BDNF mRNAs and NT-3 mRNAs. Although the reduction of NT-3 mRNA is limited to dentate gyrus of the lesion side, the induction of BDNF mRNA was observed in the lesion side firstly and then showed in the contralateral side consequently. These results support the suggestion that these neurotrophic factors may protect or support dopaminergic neurons. In addition, these data propose the possibility that neurotrophic factors may be related with degenerative diseases such as Parkinson's disease and Huntington's chorea.

Striatal c-fos levels do not correlate with haloperidol-induced behavioral supersensitivity
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The activation of cellular immediate early genes such as c-fos has been suggested to serve as markers for the undesirable extrapyramidal motor side effects of chronic neuroleptic administration. Striatal c-fos levels and stereotyped behavior have been evaluated in chronically haloperidol-treated rats which received subsequent subacute dopamine (DA) agonist treatments to investigate the possible relationship between striatal c-fos and behavioral supersensitivity (B5). Haloperidol (1 mg/kg/day for 21 days) increased apomorphine-induced stereotypies (40±3% of stereotype score compared to 23±6% in the control group) but did not modify striatal c-fos levels. The subacute administration of the DA D1 agonist SKF38393 (10 mg/kg/day for 5 days) and the combination of the D1 agonist with the D2 agonist quinpirole (1 mg/kg/day for 5 days) attenuated apomorphine-induced stereotypes after haloperidol pretreatment (to 25±4%, p<0.05, and 17±4%, p<0.01, of stereotype score respectively). The administration of quinpirole alone, however, did not modify the response to haloperidol. All DA agonists significantly increased c-fos levels after apomorphine injection (up to 200% in comparison with haloperidol alone in all cases, p<0.05). The dissociation between haloperidol-induced BS and modification of striatal c-fos levels observed in this study suggest that mechanisms different from striatal c-fos induction might be involved in the induction of BS and that striatal c-fos levels are not a good marker of this behavioral abnormality.

Normalization of movement disorders modulated by chronic pain syndromes of different origin
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Chronic pain (CP) is a multidimensional phenomenon CP intensity, CP duration and psychological changes due to CP have an influence on pain-related disability. The changes of ordinary movement scheme (OMS) are very common in patients with chronic low back pain. To investigate the level of restoration of movement disorders modulated by CP 211 patients (144 male, 67 female; age - 40±12 years), CP duration - 5.6±2.2 years, OMS disorders - 3.8±2.0, with degenerative disc disorders (L3-L4-L5 disc prolaps - 97, L3-L4 disc protrusion - 76, morbus Bechterew - 38) were treated with 0.9% saline solution (SS) used as a pain-killer (Frost, F et al. Lancet 1980;8 march 499-501) SS was injected perineurally into 24 paravertebral points at the L2-L5-S1 levels. The procedure was repeated for 12 times. Before treatment patients were graded according to the changes of OMS and CP intensity: I - low changes (115±5% patients), II - moderate changes (67±32% patients) and III - high changes (29±13% patients). After the treatment OMS was normalised in 92±43% patients. 78±37% patients were I, 23±11% patients were II and 18±9% - III. The relieving of pain restores or improves pathologically changed OMS. The CP intensity correlates with the decreased blood flow and the injected Na-ions break the pathological reflex-loop and change the activity of small nerve branches which control the microcirculation (Larsson, SE et al. Acta Orthop Scand 1990; 61:394-398). The proposed method of pain treatment could be used as an additional procedure in different neurological disorders.

 Destruction of contralateral side of the pedunculopontine nucleus reduces apomorphine-induced rotation in rats with unilateral nigrostriatal dopaminergic degeneration
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Pedunculopontine nucleus (PPN) has been considered as one of the responsible sites for apomorphine (dopamine agonist)-induced contraversive rotation in rats with unilateral dopaminergic denervation. However, this possibility has been questioned by recent results that secondary destruction of the same side of the PPN did not reduce their rotation. We investigated whether PPN lesion itself causes rotational behavior and whether destruction of the PPN contralateral to the nigrostriatal lesion affects apomorphine-induced rotation. First, we confirmed that rats with right side of the PPN lesioned with 0.5 μL of 0.1M N-methyl-D-aspartic acid exhibited contraversive circling (to the left) when they were injected with apomorphine 0.5mg/kg s.c. (85 ± 24 turns/30min, n=9). In the second experiment, rats with right substantia nigra previously lesioned with 6-hydroxydopamine (2mg/ml, 4μL) underwent the following operation. In one group (PPN lesion group, n=9) 0.5μL of 0.1M N-methyl-D-aspartic acid was injected into the left PPN to destroy this nucleus. In the other group (control group, n=7) a vehicle was injected into the same area. Contraversive rotation (to the left) induced by apomorphine 0.5mg/kg s.c. was 321 ± 26 turns/30 min in control group and 197 ± 35 turns/30 min in PPN lesion group (p<0.05). These results suggest that contralateral side of the PPN might be partly involved in the rotational behavior probably serving as a relay station for the basal ganglia output.
Control of the course of chronic diseases as well as therapy control impose great demands on standardisation. Since most neurological diseases are syndromes by nature (i.e. a certain constellation of symptoms) there are many inherent difficulties in using rating scales for scoring purposes: the symptoms are grouped to statistical factors and since patients show different profiles of symptoms, the subjects need to be combined into statistical clusters. The currently established evaluation by total sum scoring leads to the addition of different and partial independent features, thereby also ignoring statistical weights of the items. A comprehensible rating modality of clinical syndromes requires a multidimensional way of thinking. As additional problems data from rating scales in most cases only are ranked data, clinical features are reproduced only in a non linear way and - especially in multicentric applications - low interrater reliability causes an incalculable error. Thus, we do not meet the criteria required for parametric statistics, making the application of multivariate linear statistics inappropriate in most of the cases in this field.

The most promising solution of the problem of finding an adequate multidimensional non-linear regression function for the data lies in devising an approach with non-linear methods such as artificial neural nets. We applied a self-organising feature map (SOM) to training data from more than 600 patients with Parkinson's disease (PD). PD is an excellent example to examine such problems, since there is a lot of experience with a number of different rating scales and some of the symptoms can be assessed with help of instrumental methods. At first we tackled the problem of differences between raters (rating/staging scales) (Webster rating scale and Hoehn and Yahr scale). A SOM net (size 60x60 neurons) was trained both with Webster rating scale data and Hoehn and Yahr stages. As a result a prediction quality of the Hoehn and Yahr ratings from Webster rating scale data of about 90 % could be achieved. Applications of Multilayer Perceptrons confirmed this result. We carried on an extensive examination of generalisation capability (e.g. the ability of the system to classify unknown data). The SOM net was applied to compare line and astigmatism. The same type of SOM net was then applied to test data sets from an instrumental test battery (motor performance test after Schoppe), each set consisting of 28 parameters. A SOM net (size 50x50 neurons) was trained with data sets from PD patients and control persons. The result of the learning process is the clear separation of PD patients from control persons by the neural net.

### P135

**Title:** Destruction of striatal dopaminergic terminals by injection of 6-hydroxydopamine (6-OHDA) induces apoptotic cell death in dopaminergic neurons of the substantia nigra during development

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**Objective:** To determine whether programmed cell death occurs in the substantia nigra (SN) following striatal 6-OHDA injection in the developing rat brain.

**Background:** Experimental manipulations that diminish target-derived support often result in an augmented regressive event in developing neurons. There is evidence that such support is also important for the development of the SN dopaminergic system. We hypothesized that if developing dopaminergic neurons depend on target-derived trophic factors for their viability, then destruction of their striatal terminals with 6-OHDA could lead to programmed death of these neurons.

**Methodology:** An intrastriatal injection of 6-OHDA (15μg/μl) was made at postnatal day 12 (P12) in the rostral striatum of rats. At 7 days post lesion (PDL): 0 to 10 sections were processed for silver staining and for tyrosine hydroxylase (TH) immunostaining with Nissl counterstain to identify and quantify cell death in SN. In situ end labeling (ISEL) was also performed.

**Results:** Intrastriatal 6-OHDA injection in PND 7 rats resulted in augmented cell death in SN and the morphology of degenerating cells was apoptotic. Apoptosis was identified by the characteristic formation of a 10-20 μm rounded cell with distinctly bounded chromatin clumps on both Nissl and silver stain, and by TUNEL staining. At PND 10, the majority of apoptotic cells were dopaminergic. Conclusions: Intrastriatal dopaminergic terminals are associated with augmented apoptotic cell death in the SN of immature rat brains. This result supports the hypothesis that developing dopaminergic neurons are dependent on target-derived support.

### P136

**Title:** Reversal of behavioural abnormalities in a rat model of striatal neuronal degeneration following intrastriatal transplantation of pure mesencephalic and mesencephalic-striatal grafts

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We have previously shown that unilateral 6-norepinephrine (6-OHDA) lesioning of dorsolateral striatum in 6-19 age dopamine (D-ODHA) pre-treated rats results in enhanced spasticity and tachypnea-induced rotation and loss of contraversive apomorphine-induced rotation. This characteristic rotational response can be partly restored by mesencephalic-striatal co-grafts but neither by pure striatal nor sham-grafts. In the present study, we compared the behavioural effects and histological appearance of surviving dopaminergic neurons in double-lentored rats receiving pure mesencephalic or mesencephalic-striatal co-grafts 6-OHDA was administered into the left medial forebrain bundle of adult Wistar rats, followed 3-4 weeks later by injection of QA into the ipsilateral striatum. Subsequently, the lesioned striatum was implanted with fetal CNS allografts consisting of cell suspensions derived from striatal primordium and ventral mesencephalon or from lateral alone. Both groups of rats showed a reduction or reversal of apomorphine-induced rotation. This was not observed in animals receiving sham-grafts alone. Apomorphine-induced contraversive rotation was partially restored in all three groups. Tyrosine-hydroxylase (TH) immunostaining revealed graft survival in most animals. TH-positive cell numbers ranged between several hundred and thousands in both graft groups. Dopaminergic cell survival was statistically determined in animals receiving pure mesencephalic grafts compared to co-grafted animals. However, reinnervation of lesioned adult striatum seemed limited in both groups. There was no significant relationship between the number of surviving TH-positive neurons and the degree of behavioural recovery as measured by apomorphine-induced rotation. We conclude that restoration of behavioural recovery in grafted (6-OHDA) and QA pretreated animals requires survival of fetal dopaminergic neurons. However, relatively poor mapping of dopaminergic cells in pure mesencephalic grafts, limited reinnervation of lesioned adult striatum and absent correlation between number of surviving dopaminergic cells and degree of behavioural recovery indicate a diffuse rather than synaptic release of dopamine in this transplanted model.

### P137

**Title:** Motor skills in children with specific language impairment

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**Introduction:** Children with specific language impairment (SLI) by definition have no underlying neurological disease, normal nonverbal intelligence, and no hearing loss. The term "specific" implies a pure language deficit. However, the underlying nature of SLI has not yet been identified. The question of this study was, whether SLI children with mainly grammatical deficits (grammatical SLI) have an additional deficit of motor skills.

**Methods:** For assessment of normal nonverbal intelligence and a definite grammatical language deficit 19 SLI children (9 girls, 10 boys, mean age 8,8 years, range 8,1 to 10,3 years) were tested by linguistic (Heidelberger Sprachentwicklungs-test) and psychological tests (CFT 1, Raven Matrices Test). For detailed motor examination we used a computer based motor performance series (Wiener Testsystem, Schuhrfried, Austria) in the 19 grammatical SLI children and an age, gender, and handedness matched control group. Three different motor tasks were performed with both hands: 1. An open loop tapping task. 2. Aiming movement over consecutive targets. 3. Pegboard transportation as a more complex movement requiring a detailed sensor motor control.

**Results:** There was no significant difference of lateralization of motor skills between the two groups. Furthermore the tapping and aiming tasks were normally performed in SLI children, but the more complex repetitive pegboard movement was significantly impaired in the grammatical SLI children for right (p=0,01) and left (p=0.03) hand.

**Conclusion:** Grammatical SLI children have motor deficits in complex repetitive movements with sensory control. Consequently grammatical SLI is not an isolated language deficit.
Quantitative analysis of the gait pattern in infants
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Introduction: Quantitative analysis of gait provides insights into underlying conditions of the developing nervous system and offers a diagnostic tool in pathological gait patterns (e.g., cerebral palsy).

Methods: We have introduced a computer-assisted dynamic version for quantitative analysis of gait pattern (Computer Dyon Graphy CDG, Infotronic, The Netherlands) in 54 1-5-year-old infants. This gait analysis system is based on the measurement of forces under the feet. It consists of a pair of shoes, each with 8 force transducers distributed over the soles. The force values of each sensor are sampled with a rate of 50 Hz during 20 seconds walking phase. The data enable a calculation of the step time parameters, the stability, the symmetry of gait and the on-line measurement of the heel-toe process during walking.

Results: Velocity, step length per height and step frequency increased over age. Step symmetry was already achieved in the 1-year-old infants. The double support time in percent of the duration of the gait cycle decreased with age. The least decrease was recorded in 1-year-old infants. Furthermore, the heel-toe process of the 1-2-year-old infants significantly differed from that of the 3-5-year-old.

Conclusion: Our data support that important changes of gait occur in the first 3 years of life. Specially the force reaction values showed that the adaptive heel-toe process is achieved after the end of the 2nd year of life. This gait analysis system is useful in diagnostic of movement disorders.

Dopamine-melanin induces apoptosis in PC12 and neuronal cell: possible implications for therapeutic approaches in Parkinson's disease
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The presence and function of neuromelanin in the dopaminergic nigrostriatal neurons remain enigmatic. Some studies associate it with the vulnerability of nigral neurons of patients with Parkinson's disease (PD), while others regard it as a protective factor, scavenging oxygen free radicals. We exposed PC12 cells and mouse cerebellar neurons to synthetic dopamine-melanin (DA-M) and analyzed the cellular and genetic changes. Trypan blue exclusion assay and "H-thymidine uptake showed 50% PC12 cell death on exposure to 20ug/ml for 24 hrs; neutral red staining showed 50% mouse cerebellar cell death on exposure to only 10 ug/ml. Mode of cell death was apoptotic, manifested by a typical DNA-laddering, and positive DNA end-label histochemical staining in the TUNEL method. Thioli-containing antioxidants, such as reduced glutathione (GSH) and N-acetyl cysteine, and free radical spin trap agents, particularly of OR radicals, such as mannitol and N-butyl-phenyl-nitrone (PBN) showed marked protection against DA-M toxicity. We conclude that DA-M may induce typical apoptotic cell death which can be inhibited by specific antioxidants. These findings may have implications for future neuroprotective therapeutic approaches to PD.
Several pre-clinical and clinical data have recently shown that serotonin (5-HT)/dopamine (DA) interaction within the basal ganglia may represent a new target for the development of an improved therapy of extrapyramidal diseases. Although it is known that 5-HT neurons coming from the dorsal raphe nucleus (DRN) are able to modulate nigro-striatal DA activity, the neurochemical basis of this interaction remains unclear.

In the present work, we investigated in vivo the role of endogenous 5-HT in the control of DA nigro-striatal system activity using intracerebral microdialysis coupled to HPLC-ECD. A probe (CMA11/3mm) was implanted into the right striatum of halothane-anaesthetized rats and perfused with an artificial CSF (NaCl 145, KCl 2.7, CaCl₂ 1.2, MgCl₂ 1 mM, pH 7.4) at a constant flow rate of 2μl/min. In some experiments, an unipolar electrode was lowered into the RDN as well. 90 min after the probe implantation (stabilization period), striatal DA and DOPAC extracellular contents were monitored in 15 min dialysate fractions following the local infusion of citalopram (1, 25μM, 75 min), a 5-HT uptake inhibitor, or after the electrical stimulation (100μA, 1ms, 0, 5, 10 and 20 Hz during 15 min) of RDN, two conditions known to enhance endogenous 5-HT extracellular content. DA release was not modified by 1 μM citalopram, whereas a significant enhancement (+10%) was observed after 25μM citalopram infusion. However, such an effect was not blocked by the lesion of 5-HT neurons (98% depletion of 5-HT striatal content) induced by the injection of 5.7-dihydroxytryptamine (6μg/μl) into the DRN 20 days before dialysis experiments. 20 Hz, but not 5 or 10 Hz, electrical stimulation of DRN elicited a significant reduction of striatal DA release (-22%) peaking in the dialysate fraction collected during the stimulation. DOPAC output was enhanced in a frequency-dependent manner after 10 (+10%) and 20 Hz (+23%) stimulation, reaching its maximum 15 min after the cessation of stimulation.

The obtained results indicate that, in contrast to the facilitatory effect elicited by intrastriatal exogenous 5-HT (Bonhomme, N et al., Neuropharmacology 1995, 2(3) 269-279), striatal exogenous 5-HT does not affect DA release. Moreover, it appears that central 5-HT system exerts a mainly inhibitory control on striatal DA transmission, likely related to its action on DA neurons within the substantia nigra.

Oxidants may play an etiological role in Parkinson's disease by injuring nigrostriatal neurons. Treatment with levodopa might exacerbate this injury by elevating oxidative stress because of increased dopamine turnover. Oxidants can attack cell constituents (e.g., proteins, lipids, nucleic acids). 8-Hydroxydeoxyguanosine (8-OHdG), a product of oxidative damage to deoxyguanosine (dG) residues in DNA, can be assayed using HPLC with electrochemical detection (Shigenaga, MK et al., Methods in Enzymology 1994, 254:16-33) to determine an index of oxidative damage. We measured the levels of 8-OHdG (normalized with the levels of 2-DeG from the same sample) in five brain regions of male Sprague-Dawley rats (initially 294 g, n=3/4/group injected twice daily for 40 days with dopa methyl ester/benserazide (50 and 12.5 mg/kg, i.p.) or vehicle (0.9% saline, 1 ml/kg, i.p.)). Rats were sacrificed 24 hours or seven days after the last injection, and total cellular DNA from the five regions was isolated, digested, and analyzed. There are differences in the amounts of 8-OHdG in various brain regions, but levodopa treatment has no effect. There are no differences between the levels at the two times for each region. The substantia nigra contains the largest amount (14.4±1.8 μmol/8-OHdG / mole dG, means±SEM), followed by the striatum (12.1±1.4), the frontal cortex (10.5±1.0), the hippocampus (9.4±0.8), and the cerebellum (8.8±0.6). The nigral level is significantly greater than the levels in cortex, hippocampus and cerebellum. The level of 8-OHdG parallels the amount of dopamine in these areas, suggesting a possible association between dopamine levels and oxidative damage. The lack of effect of treatment with levodopa upon 8-OHdG levels may be due to several factors: normal (unlesioned) rats may be able to compensate for the additional levodopa; the amount of additional 8-OHdG formed may be too small to be measured; prolonged treatment might be necessary to induce a detectable difference; dopa-induced damage might selectively affect mitochondrial DNA, making it difficult to detect.

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Role of endogenous serotonin in the control of dopamine release in the rat striatum: an in vivo microdialysis study

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P143
Regional levels of 8-OHdG, a marker of oxidative damage to DNA, in rat brain and the lack of effect of chronic levodopa treatment.

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P144
Anticipatory silent period preceding dynamic load perturbation—feedforward control of proprioceptive feedback?

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When a dynamic load perturbation, p.e. a brief hammer tap was applied to the forearm by the subject himself, the tonic activity of the forearm flexors was clearly reduced during the 40 - 100 ms prior to the impact. This anticipatory silent period (ASP) could be observed in all forearm flexors and even extensors but it was more apparent in the biceps muscle. The ASP occurred even when the active tapping movement was unexpectedly arrested before the hammer hit the target forearm. It did not occur when the experimenter performed the tap. The ASP could be observed also in the lower extremity, p.e. the knee extensors and the plantar flexors.

As the ASP does not counteract the perturbation, its function cannot be the stabilization of the limb. Reduction of the impact by decreased muscle stiffness seems also not to be the function as the main resistance to the tap is the forearm inertia. On the receptor level, the function of the ASP could be to avoid exaggerated afferents following the impact. However, in experiments with standardized perturbations generated by torque motors we observed no decrease in the proprioceptive reflex responses.

Since the ASP can be observed in flexors and extensors, the function could be a feedforward control of mechanoreceptors at the joint by a brief decrease in joint tension.

P145
Control of pressure in skilled handwriting

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Patients with a disturbance of handwriting movements often exhibit excessive pressure on the writing surface. The question is whether an increase of writing pressure necessarily causes a decline of fluidity in handwriting movements. The handwriting movements and the writing pressure of 20 normal subjects were recorded using a digitizing tablet (Wacom UD1212) connected to a PC. In the experiments word length, letter joining, attention to vision and voluntary increase of pressure were varied. For quantitative analysis, the written trace was segmented in subsequent up-and-down strokes. Strokes can be considered fundamental units of handwriting movements. In skilled handwriting, the generation of such strokes are found to be invariably associated with smooth and single-peaked (approximately bell-shaped) velocity profiles. These are the defining characteristics of automated movements, which are conceptualized as being pre-programmed before execution of the movement. In contrast, multi-peaked velocity profiles may either indicate a disturbance of the movement or reflect control during execution. In normal handwriting no effects of word length on the automation of movements or on writing pressure were found. Under these conditions skilled writers usually join no more than 2-3 letters. However, if subjects were instructed to join all letters in a specific word, pressure increased with word length and the automation of stroke production was increasingly disturbed. Attention to visual feedback which was induced by the instruction to foveate the pen tip while writing resulted in an increase of writing pressure and an immediate shift from automated to controlled movements. When we instructed subjects to increase writing pressure voluntarily, they were able to do so without any substantial effect on the automation of movements. Therefore, it is concluded that changes in writing pressure have no desastrous effect on automation by itself, but only in combination with other factors (attention to vision, forced letter joining) which are known to hamper automation in handwriting.
Expression and characterization of huntingtin in N-ter2 neurons

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Huntington's disease (HD) is an inherited, neurodegenerative disorder caused by an expanded CAG repeat in a gene coding for a protein designated huntingtin. The protein is approximately 350 kdaltons in molecular weight and is widely expressed in neuronal and non-neuronal tissues. The normal intraneuronal function of this molecule as well as the neuropathological mechanism inherent in its expanded polyglutamine repeat sequence are unknown. In order to explore the function and test hypothetical mechanisms of pathogenicity, specific antibodies and an in vitro model for neuronal function have been developed. Fusion proteins from selected regions of the huntingtin protein have been used as antigens to generate specific polyclonal antisera. A human teratocarcinoma cell line (N-ter2/c1.D1) has been terminally differentiated into a neuronal phenotype (NT2-N) and expresses multiple markers characteristic of mammalian CNS neurons. Western blot analysis of the NT2-N cells demonstrates the presence of the 350Kd huntingtin protein. In addition, metabolic labeling with [15S]-methionine followed by immunoprecipitation using anti-huntingtin antibodies confirms the presence of the HD protein within this cell line. This system is being used to study the expression, turnover, subcellular localization and post-translation processing of huntingtin before and following exposure to neurotoxins putatively implicated in the pathogenesis of HD. These results indicate that the NT2-N cells provide a novel and important in vitro model for the study of the HD protein.

GLUTATHIONE PEROXIDASE ACTIVITY IN ALZHEIMER'S DISEASE BRAIN, Stanga-D3, Vreeko K1, Birkmayer J.G.D.1, and Reibnegger G.1, Institute for Medical Chemistry, University of Graz, Harrachgasse 21, 8010 Graz, Austria. 2 BIPET, Birkmayer Institut fur Parkinsontherapie, Schwarzenpfeilstrasse 15, 1090 Wien, Austria

Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease (AD) are major human neurodegenerative disorders, the etiologies for which remain unknown. Although a unique subset of neurons is particularly affected in each of the three diseases, they have several intriguing overlapping similarities. The motoric impairments accompanied with other parkinsonianlike symptoms are observed in 50% of the AD patients. On the other hand, parkinsonian patients develop symptoms of dementia. As defective antioxidant scavenging system plays a major role in one of the theories of the pathogenesis of Parkinson's disease and the brain is particularly susceptible to free radical attack because it generates more of these toxicants per gram of tissue than does any other organ, the aim of this study was to investigate whether and in which brain regions there is a difference in antioxidant activity between AD and control patients. Using the spectrophotometric procedure (Zhang L et al. Biochim.Biophys.Acta 1989; 1006: 140-143) the activity of glutathione peroxidase, the main antioxidant enzyme of the brain, was measured in seven brain regions (globus pallidus, putamen, nucleus amygdalae, nucleus caudatus, substantia nigra, gyrus cinguli and raphe) of postmortem brains from eight histologically verified cases with AD and 6 histologically normal controls. Showing reduced activity of glutathione peroxidase in all seven brain regions: globus pallidus (14 %), putamen (27 %), nucleus amygdalae (18 %), nucleus caudatus (24 %) substantia nigra (29 %), gyrus cinguli (11 %) and raphe (8.5 %), our results strongly support the hypothesis that AD could result from an inability to protect against accumulated damage by free radicals due to oxidative stress. It remains, however, to be determined whether oxidative stress participates to the cause of the disease or represents a consequence of nerve cell death.

Changes in electromyographic silent period in focal hand dystonia as revealed by Transcranial Magnetic Stimulation

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Focal hand dystonia is characterised by involuntary muscle contractions leading to abnormal movements generally occurring during voluntary activity. It has been shown that patients with writer's cramp as well as patients with generalised dystonia exhibit reduction of reciprocal inhibition. They also exhibit abnormal blink and H reflex recovery curves, which altogether suggests the existence of generalised disorder characterised by lack of inhibition or hyperactivity of brain structures concerned with motor activity. One of the approaches to reveal changes in cortical excitability is to study electromyographic silent period (SP) evoked by transcranial magnetic stimulation (TMS). Recent evidence shows abnormal reciprocal inhibition as well as SP shortening in other Bilateral disorders such as Parkinson's disease. Therefore we examined changes in SP duration following TMS set at 20% above the motor threshold, in 6 patients suffering from writer's cramp during two paradigms: 1) performing dystonic movement and 2) voluntary isometric contraction of the muscles mostly involved in the dystonic movement. Mean background EMG just preceding (200 ms) the stimulus was also measured and correlated to SP duration. Changes in SP were also examined, under the same conditions, on the opposite healthy side and the results compared. In spite of great intra and interindividual differences, in 5 patients, SP duration was significantly shorter when performing both dystonic and voluntary contraction of the affected hand compared to SP duration on the healthy side, while in one subject SP was nonsignificantly prolonged. Although it has been previously shown that SP duration is largely dependent of the intensity of stimulation, but not of the intensity of contraction, we found significant negative correlation between the mean preceding EMG and SP duration on the dystonic side. These results confirm previous observations that central inhibitory mechanisms are abnormal in patients with focal dystonia, most probably indicating lower inhibitory input to motor cortex either from basal ganglia or other intracortical structures.

Heat-shock protein induction following intrastriatal QA injection

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Intrastriatal injection of quinolinic acid (QA) leads to an excitotoxic degeneration of striatal projection neurons. Glial activation in striatal target regions such as the substantia nigra (SN) has been described in this model (Topper et al., 1993). In the present study neuronal responses in the SN were investigated using quantitative immunoblotting of different members of the heat shock protein family. Following unilateral injection of 240 nM QA or solvent into the rat striatum Western Blot analysis of the striatum and the SN was performed after survival times of 1, 2, and 3 days. A differential regulation of constitutive hsp 70 and grp 78 (glucose-regulated protein 78 kD), which is an indicator for overall cellular activity, was observed. In the striatum, there was an increase of grp 78 at day 1 and of hsp 70 at day 2 which reflects the excitotoxic degenerative process of striatal neurons. In the SN, no significant changes of hsp 70 could be observed. There was, however, an induction of grp 78 at day 1 and 2. It is concluded that striatal degeneration is accompanied by changes in neuronal activity in the SN which is reflected by heat-shock protein induction.

Reference: Topper R et al. Exp Neurol (1993): 123: 271-283
Changes in responses to transcranial magnetic stimulation (TMS) during submaximal voluntary contraction (60% MVC) of the adductor pollicis muscle and the subsequent recovery period have been studied in patients suffering from Parkinson disease. TMS at twice the motor threshold was applied during the sustained contraction, as well as, both at rest and during short-lasting (2 s) 60% MVCs, before and immediately after the sustained contraction, and at five minute intervals during the recovery period. Effects of muscle fatigue on the responses to TMS differed markedly from those found previously in normal subjects. In the majority of the patients no changes occurred in motor evoked potential (MEP) magnitude (peak and area) of both the agonist adductor pollicis and the remote brachioradialis muscle, either before or after the endurance point. Changes in silent period (SP) in EMG of the adductor pollicis muscle differed widely among the subjects, showing either an increase (4 subjects), a decrease (one subject) or no changes (6 subjects) in duration. Only the changes in SP duration in EMG of m. brachioradialis were similar to those found in normal subjects, showing an increase either from the beginning of the sustained 60% MVC or from the endurance point. Neither MEPs nor SPs elicited during the recovery period differed significantly from the controls. These results indicate that in muscle fatigue both excitatory and inhibitory central mechanisms in Parkinsonian patients differ from those in normal subjects.

**P152**

**The Purpose of the Preparatory Lateral Body Motion in Stepping**

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Before taking a step forwards, subjects accelerate their body-mass laterally towards the forthcoming support side and it is often assumed that the purpose of this is to bring the body into a position in which it is stable over the single support limb during the step. However we have found that, typically, the centre of mass is not displaced sufficiently to bring it directly over the support foot and that therefore subjects are unstable and accelerating sideways away from the support side throughout the step. We have suggested that the preparatory lateral motion during stepping constitutes a 'throw' of the body mass towards the support side which slows the rate of the sideways fall (Lyon, I.N. & Day, B.L. Proceedings of the Physiological Society, Oxford 1995).

A number of observations support this hypothesis. When subjects step diagonally (forwards and out to the side) the preparatory lateral motion is smaller than when stepping forwards. This is as predicted since the sideways fall does not need to be slowed as much in the diagonal step. Also, when subjects step forwards at different speeds, the magnitude of the preparatory lateral motion varies with the step duration. Again this is as predicted: as step duration reduces, the sideways fall has less time to develop and therefore needs to be slowed less.

Most recently we have investigated steps of varying stride length. Subjects stepped with 3 stride lengths, normal, larger than normal, and smaller than normal. As stride length increased so did step duration (330 ± 15ms, 380 ± 9.5ms, 440 ± 20ms [mean±SE]: ANOVA with repeated measures, p<0.005), and the lateral velocity at toe-off (93 ± 11mm/s, 112 ± 12mm/s, 122 ± 13mm/s; p<0.001). Thus the size of the preparatory throw (lateral velocity at toe-off) increased with step duration which again is as predicted by the 'throw' hypothesis.

We suggest that subjects are controlling their movement in the frontal plane during a forwards step in a ballistic manner. Balance is voluntarily relinquished but at the same time the body is thrown in such a way that the resulting motion is appropriate for the intended step (direction, speed etc.). Difficulty with the predictive nature of this type of control may contribute to the problems experienced by many neurological patients when trying to walk.

**P151**

**Lipid peroxidation and neuroprotection in the dopaminergic toxicity of 1-methyl-4-phenylpyridinium ion: evidence for a free radical mechanism in MPTP neurotoxicity**

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Using a modified microdialysis procedure, we demonstrated that intrastratal infusion of MPP+ (5 mM) induced dopamine overflow and increased formation of hydroxyl radicals (8.96 ± 2.75 pmol) as reflected by salicylate hydroxylation in the rats. Moreover, MPP+ (3.75-30 mM) also induced a formation of fluorescent products of lipid peroxidation in a dose- and time-dependent manner as measured in chloroform-methanol extracts of rat striatum. The increase of lipid peroxidation was consistent with the dopamine deficiency elicited by MPP+. Antioxidants such as U-78517F (a vitamin E analogue and potent inhibitor of lipid peroxidation) and dimethyl sulfoxide (a hydroxyl radical scavenger) significantly prevented the breakdown of tyrosine hydroxylase mRNA and inhibited dopamine depletion induced by MPP+ in the substantia nigra. These findings suggest that cytotoxic hydroxyl radicals generated from the oxidation of released dopamine induced by MPP+ may be a contributor to the nigral cell death in MPTP-parkinsonism.
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**Vestibular-evoked lateral tilt of body segments when sitting**

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One approach to testing postural mechanisms in neurological patients who have difficulty standing is to design tests applicable to the seated subject. In standing subjects, galvanic vestibular stimulation (GVS) induces a stereotyped sway of the body towards the anodal ear. Although the observed body motion stems largely from movement at the ankles, we have shown that there are additional movements of the trunk relative to it. Keeping the head relative to the trunk, that are best described by changes in the tilt angle of each body segment (Séverac Cuqau et al. Proc. of Physiol. Soc., Cork, 1995). Furthermore, we have shown that the relative tilts of adjacent body segments remain approximately constant when standing with different stance widths in which the amplitude of the leg response is dramatically changed. In the present work we investigated whether GVS induces body motion when seated and whether the relative tilts of the trunk and the head remain the same compared to a standing task. A 0.7 mA direct current was passed across the mastoid processes of 10 healthy subjects for 4 s. The protocol consisted of 4 conditions: standing with feet 16 cm apart or sitting on a stool (head always facing forwards), and 2 polarities of stimulation. 10 trials were recorded for each condition. To describe the lateral body tilt, we measured average tilts of the head, trunk and hips in the frontal plane as a function of time, using a Selspot system. As the tilt of a body segment in space results from the sum of the tilts of segments below it, we measured relative tilts, i.e. the difference between two adjacent segments. At the onset of the stimulus, all subjects showed a body tilt towards the anode side, both when standing and sitting. However, for all body segments, the maximum GVS-induced tilt was larger in standing than in seated subjects. The maximum tilt of the head relative to the trunk decreased from 0.3°±0.07 (mean±sem) when standing to 0.19±0.02 when sitting (ANOVA with repeated measures, p=0.004). The maximum tilt of the trunk relative to the hips diminished from 0.5°±0.09 (standing) to 0.27±0.04 (sitting), (p=0.005). Maximum tilt of the hips decreased from 0.15°-0.10 (standing) to 0.07±0.01 (sitting), (p=0.018). These results suggest that vestibular information is used to help control posture when sitting. However, the vestibular induced tilts of upper body segments are smaller when sitting than when standing. We suggest that the central gain of vestibular induced postural adjustments is reduced when changing from a sitting to a standing posture.

P155

**Deafferentation and corticospinal excitability in man**

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Using transcranial magnetic stimulation (TMS) it has been shown that peripheral deafferentation increases the excitability of the corticospinal projection to muscles proximal to the block. Previous studies have used cortical mapping, in which a constant stimulus is given to many scalp sites, to demonstrate this effect in relaxed muscle. Here we show that the same phenomena can be observed by studying the input-output characteristics of the motor cortex. TMS was given to the optimal scalp site at a range of intensities (30-80 %) in six normal volunteers. Responses were recorded from the left biceps muscle before and during ischemic occlusion of the left hand. In all subjects the slope of the relationship between cortical stimulus intensity and size of the EMG response increased during ischemia if experiments were conducted in the relaxed state. In contrast, ischemia had no effect on the slope of the input-output relationship when tested during minimal tonic voluntary activation of the biceps muscle.

Five subjects were studied on more than one occasion. The significant increase in corticospinal excitability seen in relaxed muscle on the first testing occasion became less obvious in subsequent sessions. Using a stimulus intensity of approximately 20 % above relaxed threshold there was an average increase in response size of 120±55 % during ischemia on the first occasion, while on the second occasion there was a minimal reduction in response size of 9±44 % (Student's paired t-test, p=0.01, comparing initial and second session testing).

The conclusions from these studies are that (i) intensity curve measurements can give similar information about corticospinal excitability as mapping techniques, (ii) changes seen in excitability with relaxed muscles are not apparent when the target muscle is active, and (iii) the changes observed in relaxed muscle become less obvious on repeated testing. These findings lead us to suggest that the changes in corticospinal excitability which are observed may have little functional relevance.

P156

**FREE RADICAL ANIMAL MODELS FOR PARKINSON RESEARCH: NITRIC OXIDE (•NO) VERSUS HYDROXYL RADICALS (•OH)**

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We investigated pathophysiological role of free radicals such as •NO (generated by •NO donor compounds) and •OH (generated by iron or manganese, MPTP/MPP+ and 6-OH-dopamine) in causing nigrostriatal degeneration in parkinsonian animal models. Surprisingly, iron promoted while manganese (1-10 mM) suppressed oxidant stress/injury in substantia nigra dopaminergic neurons. Intranigral infusion of •OH but not •NO generating compounds caused acute peroxidation of brain lipids and chronic nigrostriatal injury reflected by reduction of striatal dopamine levels. This •OH-induced oxidative brain injury was dose-dependently prevented by co-administration with antioxidants (U-78517F), atypical antioxidants (manganese and •NO) and •NO donor compounds (SNAP and GSNO). These antioxidative, neuroprotective properties of S-nitrosothiols seem to be mediated by the release of •NO because light-exposed •NO donors which can no longer release •NO were ineffective. The commonly used •NO donor SNP is a ferricyanide complex which also generate CN- and •OH leading to oxidative brain injury. The present in vivo data consistently demonstrated that •NO prevents brain injury caused by •OH. Thus, in addition to a role in cell to cell signaling, •NO may be a potent antioxidant in the central nervous system. In conclusion, •OH but not •NO radicals mediate degeneration in parkinsonian animal models. (for correspondence: e-mail: chueh@helix.nih.gov, FAX: 1-301-402-0188)

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**Autoantibodies to heparin-binding protein 3 kb at serum of patients with Wilson's Disease**

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The aim of our investigation was to identify proteins and autoantibodies to them involved in mechanisms of nervous tissue destruction at different neurodegenerative diseases. Membrane structures of perinatal human brain, taken within 1 hour after death, were solubilized by octyl-glucopyranoside. Then affinity chromatography on column with heparin-agarose was carried out. Elution was performed by 1 M NaCl. This fraction is known to contain many trophic factors. Immunoblotting of this preparation was performed with sera of patients with Wilson's Disease, Dystonia Musculorum Deformans, Friedreich's Ataxia, Parkinson's Disease, Oligopontocerebellar Degeneration and health donors. Each of 5 tested serums of patients with Wilson's Disease revealed in this fraction antigen 43 kDa, creating major band. The other serums, including health donor's one, didn't react with this preparation at the level of this method's sensitivity. The suggestion about the certain role of autoantibodies to heparin-binding membrane protein 43 kDa of human nervous tissue in pathochemical brain's changes typical for Wilson's Disease was made.
Blockade of rotational behavior induced by D1/D2 dopamine agonists through the administration of "antineuro" oligodeoxyribonucleotides directed against rat brain D1 receptor mRNA

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"Antineuro" oligodeoxyribonucleotides are new pharmaceutical tools designed to specifically inhibit, through mRNA hybridization, the synthesis of any cloned receptor (Waldherr, TIPS 1994:15:42). We studied the effect of repeated administration of an "antineuro" oligodeoxyribonucleotide (DIR-asi) construct designed to hybridize the D1 receptor mRNA on the rotational behavior induced by dopamine agonists in rats with either a unilateral striatal quinolinic acid lesion (normosensitive) or a unilateral median forebrain bundle 6-OHDA lesion (supersensitive). Following 6 intracerebroventricular injections of DIR-asi (2.5 moles every 12 h) there was a 95% inhibition of rotational behavior induced by the D2 receptor agonist, LY 171555 in both supersensitive and normosensitive rats. The doses of the D2 agonist used were 0.1 and 10 mg/kg, ip, 10 h after the last injection of DIR-asi, for each model respectively. A 100% inhibition of the responses induced by the D1 agonist SKF 38393 (2 mg/kg, ip, 10 h after the last administration of the "antineuro" oligodeoxyribonucleotide) was observed using the same administration schedule of the DIR-asi construct in supersensitive rats. In both cases the inhibition was dose-dependent. Our results confirm the crucial need for D1 receptor activation to induce rotational behavior in both normosensitive and supersensitive rats, and the value of this new pharmaceutical tool in the analysis of dopamine receptor interactions.

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D-DOPA and DHPPA increase striatal dopamine and turning in rats: an in vivo cerebral dialysis study

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The D stereoisomer of levodopa (D-DOPA) and its α-keto acid metabolite 3,4-dihydroxyphenylpyruvic acid (DHPPA) significantly increased in vivo extracellular dopamine levels when perfused into the striatum. Following D-DOPA and DHPPA administration, the cumulative increase in dopamine levels was 30% and 11% respectively that of L-DOPA. Rats with unilateral 6-hydroxydopamine induced lesions of the substantia nigra demonstrated brisk contralateral turning following each compound. The turning, however, was delayed 10-20 min and total turns were 40-60% less following D-DOPA and DHPPA than following L-DOPA.

Conclusion: D-DOPA can be metabolized in vivo within the brain to dopamine possibly via a transamination pathway in which DHPPA serves as intermediary metabolite. Possible implication for the treatment of Parkinson’s Disease will be discussed.

Apoptosis in animal models of neurodegenerative disease

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Programmed cell death (PCD) plays a major role in the differentiation and development of the central nervous system (CNS). Most types of PCD in the CNS exhibit morphological and biochemical features of apoptosis, i.e. chromatin condensation and DNA fragmentation in oligonucleosomal multiples of 180-200 base pairs. Few in vivo data are available on apoptosis in neurodegenerative disease. We therefore used an in situ end labeling to study (1) genetically determined cell death in the cerebellar cortex of the mutant mice lurcher (lc) and weaver (wv) and (2) neurochemically induced dopaminergic cell death in rats after intranigral injection of 6-OHDA and in mice after systemic treatment with MPTP.

lc is an autosomal dominant mutation located on chromosome 6, that resembles human adult dominant ataxia in its histological and clinical features. Histologically, Purkinje cells and - to a lesser extent - granule and inferior olive neurons are affected. We is an autosomal recessive mutation, homozygous and heterozygous animals loose cerebellar granule cells during the first postnatal weeks. Homozygous animals exhibit additional pathology of the dopaminergic nigrostriatal system. In affected wv mice apoptosis occurred in Purkinje and granule cells (4.7±0.7 vs 2.6±0.9; number of granule cells per mm granule cell layer compared to age-matched littermates, mean±SEM). Affected wv mice showed increased numbers of apoptotic progenitor (granule) cells (28.0±2.1 vs 3.8±1.3), while Purkinje cells appeared not to be affected. No apoptotic nuclei were found in the substantia nigra (SN) of affected wv mice.

In MPTP-treated mice at the time point examined approximately 1% of cells per section of the SN showed apoptotic nuclei. Similar results were obtained after 6-OHDA-treatment. The low number of apoptotic nuclei detected could be due to the rapid time course of apoptotic cell death: apoptotic bodies are cleared within 2-6 h. Alternatively, the neurotoxin MTPP and 6-OHDA may induce apoptosis only in a subset of cells.

Expression of neuropeptides genes in the genetically dystonic hamster

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The site of a functional defect has yet to be identified in idiopathic dystonia. A thorough study of available animal models of dystonia should help identify neurochemical systems to be investigated in human as a basis for a rational pharmacotherapy. In the mutant hamster model of generalized dystonia, functional abnormalities in amino-acid neurotransmitter function have been suggested to play a role in development of the symptoms.

In the present study, we have sought to determine whether these abnormalities are associated with modulation in the expression of genes encoding neurotransmitter thought to be involved in movement function. Using hybridization histochemistry with 35S-ATP labeled oligonucleotides, the expression of neuropeptide genes was examined in dystonic hamsters (dt) and compared with an inbred line (iCo) of non-dystonic hamster and with a different, outbred line of Syrian hamsters (oCo). The study examined the expression of glutamic acid decarboxylase (GAD), cholecystokinin (CCK) and somatostatin (SRIF) in cortex and striatum. The distribution of these mRNAs was similar to our previous results and to published maps in the rodent. In all cortical regions studied (frontal, parietal and piriformis), the expression of CCK in dt and iCo was similar, but significantly increased when compared to oCo. SRIF expression was significantly decreased in cortex and striatum of dt as compared to both iCo and oCo. GAD expression was decreased in the striatum of dt as compared to both iCo and oCo, but similar values were found in all groups in the other regions studied (cortex, septum and diagonal band).

This study demonstrates that some changes in modulation of the expression of some peptid is can be found in the dystonic hamster, which is in contrast to some other animal models of dystonia, like the dystonic rat, where no such changes have been found.
Glutamate is the primary excitatory neurotransmitter in the CNS. It binds several receptor subtypes including the non-NMDA α-aminomethyl-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor.

We have examined the distribution and expression levels of the transcripts GluR1 to GluR4 in the developing rat basal ganglia using in situ hybridization histochemistry. Using cRNA riboprobes, our results indicate that GluR1 and GluR2 transcripts are expressed at high levels in the neonatal striatum and appear to be developmentally regulated. Adult striatal neurons showed a marked decrease in GluR1 and a more modest decrease in GluR2 transcript expression compared to neonates. Using oligonucleotide probes to differentiate the flip and flop isoforms, our results indicate that the flop isoform is the predominantly expressed transcript of both GluR1 and GluR2. Transcripts for GluR3 and GluR4 are expressed at much lower levels than GluR1 and GluR2 and do not appear to be developmentally regulated. These results suggest that differential expression of receptor subunit transcripts may confer distinct electrophysiological properties between neonate and adult striatal neurons. Such a phenomena may contribute to differences in susceptibility to disease and injury within the aging basal ganglia.

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The Developmental Expression of AMPA Receptor Subunits in the Basal Ganglia of the Rat

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Use of Pramipexole, a Non-ergot Selective Dopamine Agonist, to Evaluate Dopamine D2 Receptors in Basal Ganglia and Mesolimbic Function

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Pramipexole (PPX) is a non-ergot selective dopamine agonist with preferential affinities for the D2 receptor (Mierau et al., Eur J Pharmacol 290:29, 1995) and established clinical efficacy in Parkinson's Disease (PD). mRNA distributions suggest D2 receptor locations in mesolimbic regions, although antibody studies suggest basal ganglia locations as well. In receptor binding studies, [3H]-PPX bound with D2 affinity to Islets of Calleja (125 fmol/mgP), n. accumbens (54 fmol/mgP), olf tub (53 fmol/mgP), and caudate (49 fmol/mgP), and with D1 affinities in L. septum (77 fmol/mgP), M. septum (50 fmol/mgP), and diagonal band (43 fmol/mgP). In electrophysiology experiments, PPX, but not the D2 preferring agonist, U-91356A, excited single type II caudate neurons and inhibited SNPR firing, but was most potent in inhibiting n. accumbens neurons. U-91356A, a D2 preferring antagonist, was more potent in inhibiting PPX depression of SNPC DA neurons than it was in inhibiting PPX inhibitions in SNPR; U-91944A, a D3 antagonist, was as potent in SNPR as in SNPC. It is concluded that D2 receptors play a significant role in basal ganglia potentially useful for treating PD, but that D2 receptor activation in mesolimbic reward pathways could also be of value in treating the depression that often accompanies this disease.

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Ventral Subiculum and Nucleus Accumbens Play in Concert under Learning of Patterned Alternation in Rats

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The role of hippocampus–striatum interference in acquisition of single motor alternation (win-shift task) in T-maze was investigated in two groups of Sprague-Dawley rats following electrolytic lesion of medial area of N. Accumbens (NA) or surgical section of ventral subicular (VS) pathway projected to above area of NA. It has been shown that NA lesioned rats were completely unable to learn single alternation task used without exposition of conditioned discriminative stimuli whereas VS sectioned rats demonstrated transient impairment of this test expressed in 3–4 fold slowing in acquisition of patterned alternation in contrast to control and sham-operated animals. Both groups of operated rats however successfully learned single alternation task after introducing of sensory discriminative cues signalling about side of reinforcement. The results obtained as well as our previous data (Albertin, Golovacheva. Pfl. Arch. Eur. J. of Physiol., 1995, 410:257) give an evidence that both ventral subiculum and medial accumbens are involved in working but not reference memory related motor tasks.
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Pseudathetosis in Four Patients with Hypesthetic Ataxic Hemiparesis
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Involuntary movement is rare consequence of thalamic lesion. We report 4 patients with hypesthetic ataxic hemiparesis showing involuntary movement in hand contralateral to thalamic lesion. The involuntary movement mimicking choreoathetosis (so-called "pseudoathetosis") was thought to result from sensory ataxia because they were unable to recognize their hands in space. There was profound loss of pain, position, vibration sensation in entire hemibody contralateral to thalamic lesion, and severe left ataxia in spite of mild weakness. The abnormal movement was irregular, often jerky or writhing when they were standing or walking in 3 patients, and was like piano playing when he outstretched his hand in one, more prominent with eye closure.

Magnetic resonance imaging revealed lacunar infarction in 3 patients and hemorrhage in one in thalamus including ventroposterolateral nucleus.

P166
Metabolic changes in the Frontal Lobe of Patients Suffering from Huntington's Disease - A Proton Magnetic Resonance Spectroscopy Study
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Introduction: After an increased number of CAG-repeats has been shown to be the genetic defect in Huntington's disease (HD), efforts are concentrated on the functional consequences of the mutation, pathogenesis and future neuroprotective strategies. There is evidence that impairment of energy production contributes to the pathogenesis of striatal lesions in HD. Patients and methods: We examined 17 patients (mean age 45.6 years) with a definitive molecular genetic diagnosis of HD and 4 asymptomatic gene carriers (mean age 45.4 years). The severity of the condition was defined by using the Shoulson score and the motor score of the United Huntington's Disease Rating Scale (UHDRS). Genetic testing was performed by standard techniques, and showed that each of the patients and asymptomatic carriers had 39 CAG repeats or more. Patients were divided into four groups: group I 4 symptomatic gene carriers, group II: 6 patients (moderately handicapped), group III: 6 patients (medium handicapped), group IV: 5 patients (severe handicapped), group V: 19 healthy controls. 1H magnetic resonance spectroscopy was performed on a 1.5 Tesla Gyroscan S 15 (Philips) system. Based on a transversal T2 SE weighted imaging we selected a volume of 20x20x40 mm in a frontal area of the brain. Evaluation of the ratios phosphocholine (PCh)/phosphatidylcholine (PCh), N-acetylaspartate (NAA)/PCh and lactate/PCh by integral of the peaks allowed a quantitative description of metabolic alterations. Results: The NAA/PCh ratio was indistinguishable in asymptomatic gene carriers, moderately affected patients and controls. The differences between controls (1.8±0.37) and groups II (1.41±0.24) (p = 0.022) and IV (1.26±0.23) (p = 0.008) were statistically significant. We did not detect any lactate in the controls but in eight of the 17 symptomatic patients and each of the four asymptomatic gene carriers.

Conclusion: This study demonstrates that the neuronal marker NAA is reduced in late stages of HD. The detection of lactate supports the concept of a nucleary encoded energy deficit being part of the pathogenesis, but a clear-cut relation to the clinical course could not be detected by this study.

P167
Four Cases of Hemiballism Without Lesion in the Subthalamus Nuclei
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Hemiballism of abrupt onset is classically associated to stroke in the subthalamic nucleus (STN). Nevertheless there are some reports which show the opposite. We have evaluated four patients (3/25) with hemiballism without an evident lesion in the STN. All patients were elderly with abrupt onset of hemiballism, their mean age at onset was 72.5 years (range from 70 to 79 years). One patient had hypertension and other hypertensive and diabetic. None of the patients had antecedent of cerebrovascular disease. All the patients presented involvement of upper and lower limb and in two cases the ipsilateral facial region was also involved. The left hemibody was affected in two cases. The duration time from onset of the abnormal movement to hospitalisation ranged from one to seven days.

A CT performed in one patient showed multiple cortical metastasis with marked perilesional edema. In other two cases MRI were performed and showed in one case an isoechogenic lesion in the right thalamus and in the other multiple small infarcts in both striatum. One patient died in hospital because of a severe pneumonia and autopsy was performed. Small isoechogenic lesions were found in both thalamus.

Hemiballism is effective in two patients. In the patient with edema and metastasis, oral glycerol produced marked improvement of the abnormal movement.

We conclude that sudden onset hemiballism can have a variable etiology and be caused by lesions not only in the STN but in other different areas.

P168
Atypical presentation of Huntington's disease
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Huntington's disease (HD) is an autosomal dominant inherited disease, usually presents with chorea and dementia in the middle-aged. The diagnosis can be confirmed by detection of the expansion of (CAG)n trinucleotide repeat in the 5' region of the IT15 gene. A few atypical features of HD have been reported, including: myoclonus, dystonia, action tremor, Tourette's syndrome, and absence of dementia. We reported here three cases of HD, none of them had positive family history and all had been confirmed by the presence of expanded (CAG)n repeat. Case 1 presented with progressive deterioration of mentality and change of personality since the age of 41 years. Only minimal tremor of hands was noted during the following 6 years. Case 2 had an elderly onset at 68 years of age, presented with impairment in calculation and slow involuntary movements of the left hand. Orobuccolingual dyskinesia and parkinsonism developed next year, and were the predominant features in the following 2 years. Case 3 presented with continual, generalized chorea and episodic retrocollis since the age of 28 years. We conclude that genetic analysis for HD should be performed in any patients with bizarre involuntary movements or presenile dementing process, even without a positive family history.