Neuropharmacology

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Authors present even numbers: 1:00 PM–2:00 PM

P1131
Effects of riluzole as “rescue therapy” in a MPTP + 3-NP mouse model of striatonigral degeneration: Experimental rationale for its use in multiple system atrophy
(Bordeaux, France; Innsbruck, Austria)

Only symptomatic treatments of limited efficacy are available in striatonigral degeneration (SND)/multiple system atrophy-parkinsonism (MSA-P). We investigated the potency of riluzole, an anti-glutamatergic drug, to ameliorate degeneration process in a phenotypic MPTP + 3-nitropropionic acid model of SND/MSA-P. We used a “neuronal rescue” strategy by administering riluzole (for 7 days) only after the end of intoxication. The motor disorder, its recovery, behavioral performances at motor and sensorimotor integration tests (rotarod, pole test, traversing a beam, open-field), and histopathological outcome were compared in the control (saline, n = 7) and riluzole groups (10 mg/kg, n = 7; 20 mg/kg, n = 7), matched by triplets for motor severity. While riluzole did not produce any effect on the gross motor disorder nor on rotator task or open-field kinetic variables, riluzole allowed better recovery on the beam-traversing task and the pole test. Accordingly, the histopathological outcome was significantly better in the riluzole-treated mice regarding both nigral and dorsolateral striatal cell loss and astroglial activation, with a dose-effect relationship. Thus, riluzole induces subtle symptomatic effects but has “neuronal rescue” properties in a SND/MSA-P phenotypic animal model.

P1132
Dopamine and adenosine receptor interaction as basis for the treatment of Parkinson’s disease
M. Morelli, A.R. Carta, P. Annalisa, T. Elisabetta, S. Nicola (Cagliari, Italy)

Background: Studies in animal models of Parkinson’s disease (PD) and preliminary clinical trials have shown that adenosine A2A antagonists might be useful in the treatment of the disease.

Objective: In order to study the effect of A2A blockade on parkinsonian tremor and on long-term modifications produced by chronic L-DOPA, we have evaluated: I) the effect of the A2A antagonist SCH 58261 on jaw tremor induced by tacrine; II) GAD 67 mRNA in basal ganglia, by in situ hybridization in 6-hydroxydopamine (6-OHDA) lesioned rats chronically treated with SCH 58261 + L-DOPA or L-DOPA alone, as model of dyskinesia.

Methods: Intact rats received tacrine (2.5 mg/kg) in order to induce bursts of jaw movements. Unilaterally 6OHDA lesioned rats were treated either acutely or chronically (19 days) with L-DOPA (6 mg/kg), L-DOPA (3 mg/kg) + SCH 58261 (5 mg/kg). Turning behavior and GAD 67 mRNA were evaluated in these rats.

Results: I) Parenteral administration of SCH 58261 (5 mg/kg) counteracted the number of burst and the number of jaw movements induced by tacrine. II) Acute administration of SCH 58261 + L-DOPA, potentiates the rotational behavior induced by L-DOPA indicating anti PD activity of A2A antagonists. Chronic administration of SCH 58261 (5 mg/kg) plus L-DOPA (3 mg/kg) or L-DOPA (6 mg/kg) alone, at doses producing the same intensity of rotational behavior during the first administration, showed no changes and an increase in GAD67 mRNA in the GP respectively. Moreover, in the SNr, a significant decrease in GAD67 mRNA was observed after either treatments, however, while L-DOPA (6 mg/kg) decreased GAD67 mRNA below the intact side, SCH 58261 plus L-DOPA (3 mg/kg) brought the GAD67 mRNA level increased by the lesion, to the same level of the intact SNr.

Conclusion: The results suggest that antagonism of A2A receptors might counteracts the motor impairment and tremor which characterize PD. Moreover, long-term L-DOPA administration produces changes in basal ganglia activity which appear to be responsible of dyskinetic effects, whereas chronic administration of A2A antagonists + L-DOPA produces little or no changes in basal ganglia suggesting that this treatment has low dyskinetic potential.

P1133
Long term effects of Helicobacter pylori eradication on L-DOPA absorption in Parkinson’s disease patients
L. Brusa, A. Pietroiuisti, M. Pierantozzi, S. Galati, E. Fedele, P. Stanzione (Rome, Italy; Genova, Italy)

Objective: Evaluate beneficial effects of H. pylori eradication in PD patients.

Background: H. pylori infection may adversely affect L-DOPA pharmacokinetic in Parkinson’s disease (PD), through direct degradation of the drug and/or changes of gastroduodenal environment.

Methods: We conducted a prospective study on 25 H. pylori infected PD patients. Clinical, histologic and pharmacologic response to placebo, to standard eradication therapy or to antibiotic therapy (allopurinol), were assessed 2 weeks and 3 months after treatments (Tabl-2).

Results: H. pylori eradication (AB group n = 13, sessions T1 and T2 vs. T1, and T2) significantly improved clinical disability score and pharmacokinetic parameters (AUC, Cmax), while placebo (n = 25 between session T1 and T2), and antibiotic therapy (AO group n = 12) did not; in eradicated patients, t-DOPA Cmax significantly increased and sustained drug levels in the falling phase of the blood concentration-time curve produced a significantly increased AUC; the maximal beneficial clinical and pharmacokinetic effect was observed 3 months after eradication (T2) (Fig. 1); gastric-duodenal score decreased in parallel to t-DOPA improved absorption.

Conclusion: Our data demonstrate a H. pylori reversible interference with L-DOPA clinical effect due to an impaired absorption probably related to gastroduodenitis. We suggest a test and treat policy in the large cohort of fluctuating patients showing positivity to H. pylori infection.

TABLE 1 (P1133). Timing of procedures used in the study

<table>
<thead>
<tr>
<th>Procedure</th>
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Therapy

Placebo | Start | End |
AB therapy | Start | End |
AO therapy | Start | End |
TABLE 2 (P1133). Session time schedule in the two protocols, 0–4 hours and 0–11 hours, used in the study

<table>
<thead>
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FIG. 1 (P1133).

Reference

P1135
Entacapone increases and extends striatal dopamine release following t-DOPA/benserazide treatment in the rat
M. Gerlach, M. van den Buuse, C. Blaha, D. Bremen, P. Riederer
(Wuerzburg, Germany; Parkville, Australia; Sydney, Australia; Hamburg, Germany)

Objective: The aim of this study was to examine the effects of entacapone on striatal dopamine metabolism in vivo following treatment with different doses of t-DOPA (levodopa, L-3,4-dihydroxyphenylalanine)/decarboxylase inhibitor in the rat.

Background: The catechol-O-methyltransferase (COMT) inhibitor entacapone is used as an adjunct to t-DOPA in the treatment of Parkinson’s disease (PD) because COMT inhibition prevents the metabolism of t-DOPA to its inactive O-methylated derivative 3-O-methyl-DOPA (3-OMD). By reducing levels of this inactive metabolite, COMT inhibition improves bioavailability of t-DOPA and increases the duration of clinical response in patients with PD.

Methods: A total of 40 male unilateral 6-hydroxydopamine-lesioned Sprague-Dawley rats were divided in 5 experimental groups. One group was treated twice daily with t-DOPA (6.5 mg/kg) and benserazide (1.5 mg/kg) i.p. for 2 weeks. The other groups were treated twice daily with 10 mg/kg entacapone i.p. and different doses of t-DOPA (1.5–6.5 mg/kg) i.p. At 16–18 days of treatment extracellular dopamine levels following treatment were determined in the lesioned and unlesioned striata by chronoamperometry.

Results: In rats treated with entacapone, extracellular levels of dopamine were increased and prolonged dose-dependently following different doses of t-DOPA. Interestingly, these effects appeared greater in the lesioned striatum. Area under the curve analysis of voltammetry data demonstrated that in lesioned striatum 1.5 mg/kg t-DOPA and COMT inhibition had the same effect on dopamine release than 6.5 mg/kg t-DOPA alone.

Conclusion: This data demonstrated for the first time in vivo that the striatal dopamine release following t-DOPA treatment is enhanced and prolonged by additional peripheral COMT inhibition with entacapone.

P1136
Plasma homocysteine levels in pergolide treated Parkinson’s disease patients
S. Özkan, O. Colak, C. Kutlu, M. Ertan, O. Alatas (Eskisehir, Turkey)

Hyperhomocysteinemia is a risk factor for increased vascular disease in t-DOPA treated PD patients. This effect of t-DOPA is associated with the metabolism of t-DOPA by methylation. We aimed to assess the effect of pergolide on plasma homocysteine levels. We compared the plasma homocysteine levels between the PD patients, who were treated with pergolide as monotherapy, with t-DOPA as monotherapy, or with t-DOPA...
and pergolide combination and the controls. Plasma homocysteine levels were significantly higher in t-DOPA monotherapy group, and there were no significant differences for pergolide treatment groups. Pergolide can be beneficial for increased plasma homocysteine levels.

P1137
Levodopa raises pain threshold in Parkinson’s disease: A clinical and positron emission tomography study
C. Brefel-Courbon, P. Payous, C. Thalamas, M. Galitzky, J. Montastruc, O. Rascol (Toulouse, France)

Objective: To compare pain threshold before and after administration of levodopa in patients with Parkinson’s disease (PD) and in control subjects and to assess the effect of levodopa on cerebral activity with positron emission tomography (PET) during experimental nociceptive stimulation in these 2 groups of subjects.

Background: PD patients frequently experience painful sensations. It has been suggested that the occurrence of such painful symptoms could be in part due to central modification of nociception.

Methods: Pain threshold was determined using thermal stimulation (immersion of the right hand in cold water) during two randomized periods: OFF (after 12 hr of dopaminergic treatment discontinuation) and ON (after levodopa dose administration). We used different water temperatures from 20°C to 0°C and the subject rated intensity of the cold stimuli on a Visual Analogue Scale from 0–10. Pain threshold was defined as water temperature inducing painful sensation superior or equal to 3. We performed H11005 PET analysis of cerebral blood flow (CBF) while subjects received alternate randomised innocuous (defined as pain threshold) and innocuous (previous value plus 10°C) cold stimuli during OFF and ON periods.

Results: We studied 9 PD patients (mean age ± SD: 65 ± 8 years) and 9 control subjects (mean age ± SD: 59 ± 4 years). In OFF condition, pain threshold in PD patient was significantly lower than in controls (8 ± 3°C vs. 4.4 ± 3°C, P = 0.03). Administration of levodopa (216 ± 50 mg) significantly raised pain threshold in PD patients (8 ± 3°C vs. 4.6 ± 3°C, P = 0.007) but not in controls. In ON condition, pain thresholds were similar in PD and controls. During OFF period, there was a significant increase in pain induced-activation in right insula and prefrontal and left anterior cingulate cortices in PD compared to control group. Levodopa significantly reduced pain induced-activation in these areas in PD.

Conclusion: This study shows that pain threshold is abnormal in PD patients and returns to normal ranges after levodopa administration. Moreover, PD patients have higher pain induced-activation in nociceptive areas which can be reduced by levodopa.

P1138
Short and long term effect of low doses of botulinum toxin in 100 Tunisian patients over an 8-year period
N. Gouider-Khouja, G. El Euch, I. Turki, S. Chebel, F. Hentati (Tunisia)

Objective: To report the results of treatment with botulinum toxin (BT) in 100 Tunisian patients treated over a period of 8 years (1995–2003) with lower doses than usually used and to compare with previously reported series.

Background: BT is used in various neurological indications. Its efficacy and safety have been demonstrated in many previous studies. Recent studies aim to determine the benefit of lower doses and the long term effects in clinical practice.

Methods: One hundred patients (53 women, 47 men) were treated with BT at the Neurology Department of the National Institute of Neurology in Tunis: 66 patients had hemifacial spasm (HS), 14 blepharospasm (BS) and 20 cervical dystonia (CD). A total of 485 injection sessions have been performed (mean 4.8, extremes 1–26). The following parameters were evaluated by questionnaire and examination, 15 days after the injection: time to onset of benefit, duration of benefit, socio-professional impact of treatment, amount of benefit (expressed as percentage from 0–100) and side effects. An additional evaluation was performed before the following injection session.

Results: Among the 66 patients (29 men, 37 women; mean age of onset 43.4 ± 16 years) with HS, 67% had left HS and 33% had right HS. HS was idiopathic in 89% of cases. Mean disease duration before BT treatment was 4.6 years. A total of 368 injection sessions were performed (mean 5.5, range 1–26). Mean dose of BT per session was 90.6 ± 39 U Dysport, mean time to onset of benefit was 5.5 days, mean duration of benefit 2.8 months and mean percentage of improvement 65%. In the 14 patients (5 men, 9 women; mean age of onset 53.3 ± 21 years) treated for BS, mean disease duration before BT was 1 year. Sixty-six injection sessions were performed (mean 4.8, range 1–15). Mean dose of BT per session was 111.5 ± 23 U Dysport, mean time to onset of benefit was 3.7 days, mean duration of benefit 2.4 months and mean percentage of improvement was 60%. In the 20 patients (13 men, 7 women; mean age of onset 23 ± 17 years) treated for CD, mean disease duration before BT was 8 years. Sixty-two injection sessions were performed (mean 3.2, extremes 1–15). Mean dose of BT per session was 288 ± 168 U Dysport, mean time to onset of benefit 8 days, mean duration of benefit 2 months and mean percentage of improvement 62%. Although 20% of patients reported adverse effects at any one time during the course of treatment, this represents only 7% of all injection sessions. Main side effects (some patients experienced more than one side effect) were: headache in 7 cases, facial asymmetry in 6, ptosis in 4, blurred vision in 3, dry eyes in 2, neck weakness in 2, bruising in 2 and drowsiness in 1 patient.

Conclusion: This study confirms efficacy and safety of BT in the long term treatment of HS, BS and CD with sustained benefit over time. Relatively low doses of BT seems to give appreciatively the same benefit than higher doses. The strategy we adopted is of interest in emerging countries where the treatment with BT could seem expensive to national health care structures and could limit the accessibility of such an efficacious treatment to many patients.

P1139
Desipramine increases t-DOPA-derived extracellular dopamine in the striatum of 6-hydroxydopamine-lesioned rats
A. Arai, K. Kanmari, H. Shen, M. Baba, M. Matsunaga (Hirosaki, Japan)

Objective: To determine the role of noradrenalin transporter (NAT) in the disappearance of t-DOPA-derived dopamine (DA) from the extracellular space in the dopaminergic denervated striatum.

Background: Previous studies have demonstrated that administration of t-DOPA to rats with dopaminergic denervation results in a rapid increase in extracellular DA levels in the striatum. And once extracellular DA reaches the peak level, it decreases rapidly in the later time course. However, the mechanism underlying this rapid decrease of extracellular DA in the DA-depleted striatum remains unclear.

Methods: Using in vivo microdialysis method, we measured extracellular DA levels and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) levels in the striatum of rats with nigrostriatal dopaminergic denervation by 6-hydroxydopamine (6-OHDA). Changes in extracellular DA, DOPAC, and HVA levels following 50 mg/kg t-DOPA administration were observed under pretreatment with desipramine, a specific NAT inhibitor.

Results: Pretreatment with 25 mg/kg desipramine increased the cumulative amount of t-DOPA-derived extracellular DA in the striatum of 6-OHDA-lesioned rats to 173% of that without desipramine (P < 0.01). However, desipramine induced no changes in extracellular DOPAC and HVA levels.

Conclusion: These results suggest that extracellular DA derived from exogenous t-DOPA is at least partly taken up through NAT in the DA-depleted striatum.

P1140
Cabergoline, a dopamine agonist, prevent levodopa-induced abnormal increase of lipid peroxidation mainly due to increase of glutathione content and inhibition of caspase activities in 6-OHDA-lesioned mice
K.-I. Tanaka, N. Ogawa (Okayama, Japan)

Levodopa therapy is the gold standard for symptomatic treatment for Parkinson’s disease (PD), but levodopa or dopamine (DA)-induced neurotoxicity have been reported both in vitro and in vivo experimental study.
present study, we examined the effects of cabergoline, a DA agonist, on levodopa-induced abnormal increase of lipid peroxidation (LPO) and caspase activities in 6-hydroxydopamine (6-OHDA)-lesioned mice, to clarify the beneficial effect of combined therapy with DA agonists and levodopa in PD. Daily treatments of levodopa/carbidopa for 7 days beginning at 1 day after 6-OHDA i.c.v. injection increased striatal DA levels and glutathione (GSH) contents in a dose-dependent manner. Furthermore, high dose of levodopa/carbidopa (50/12.5 mg/kg) enhanced both LPO and caspase-3, caspase-8 and caspase-9 activities in 6-OHDA-lesioned mouse brain. However, levodopa/carbidopa (50/12.5 mg/kg) combined with cabergoline (0.25 mg/kg) canceled levodopa-enhanced caspase-3, caspase-8 and caspase-9 activities in the 6-OHDA-lesioned mouse brain. In addition, the GSH-increasing effect of combined treatment with cabergoline and levodopa/carbidopa is stronger than that of levodopa/carbidopa mono-treatment. Further, cabergoline prevents levodopa-induced abnormal increase of LPO mainly due to increase of GSH content and inhibition of caspase activities in 6-OHDA-lesioned mice.

P1141
Metabotropic glutamate 5 (mGlu5) receptor antagonist-induced locomotion requires adenosine A2A and dopamine D2 receptors and is potentiated by an A2A antagonist
A. Kuchroo, D.K. Grandy, J.-F. Chen, L. Orlando, M.A. Schwarzschild (Boston, Massachusetts, USA; Portland, Oregon, USA)

Objective: To determine whether the motor stimulant properties of mGlu5 antagonists rely on or interact with adenosine A2A and dopamine D2 receptors.

Background: A major goal of Parkinson's disease (PD) drug discovery is the development of non-dopaminergic therapies that improve parkinsonian motor deficits without the liability for the adverse chronic effects of standard dopaminergic drugs. Preclinical studies have identified antagonists of the A2A receptor and the mGlu5 receptor as promising candidates. Recent evidence has suggested the function of functional heteroreceptors containing A2A and mGlu5 receptors, as well as A2A and D2 receptors in endocannabinoid and post-synaptic elements of basal ganglia circuitry, and raise the possibility of developing synergistic pharmacological strategies to treat motor dysfunction in PD.

Methods: Locomotor stimulation by the mGlu5 antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP) was assessed in the absence of A2A and/or D2 receptors in mice or in the presence of an A2A antagonist (KW-6002). In an initial experiment, MPEP (5 mg/kg) was administered intraperitoneally in wild-type (WT), A2A receptor knockout (A2A KO), D2 KO, and double A2A-D2 KO littermates (generated by crossing double heterozygote mice; n = 6 for each genotype). In a separate experiment, the D2 agonist SKF 38393 (15 mg/kg) was also assessed in these mice. In a third experiment MPEP (5 mg/kg) or saline was administered intraperitoneally in combination with the KW-6002 (0.3 mg/kg) or its vehicle to C57Bl/6 mice (n = 5 for each of the 4 groups). Drugs were administered 2 hr after mice were placed in automated activity monitoring cages (to allow for habituation), and locomotion was recorded for one more hr.

Results: Locomotor stimulation by MPEP, expressed as distance traveled (for 1 hr post-MPEP less 1 hr pre-MPEP), was significant in WT mice (85 ± 12 cm [mean ± SEM]; P < 0.05, post vs. pre) but not in the A2A (25 ± 3 cm), D2 (15 ± 7 cm), or A2A-D2 KO (10 ± 2 cm) mice. By contrast, locomotor stimulation by the D2 agonist SKF 38393 was significant in all four genotype (and not appreciably different in the receptor KO mice compared to their WT littermates), suggesting specificity of the A2A and D2 receptor-dependence for motor modulation by the mGlu5 receptor. In the third experiment, MPEP alone exhibited a motor stimulant effect, whereas the A2A antagonist KW-6002 alone at the low dose employed here did not stimulate locomotion. However, MPEP plus KW-6002 increased locomotion to an extent significantly greater than did MPEP alone.

Conclusion: The dependence of mGlu5 antagonist-induced motor stimulation on both A2A and D2 receptors, and its potentiation by an A2A antagonist highlight the functional interdependence of these receptors and provide a rationale for a combinational drug strategy for enhancing motor function. Given the present findings and the restricted regional and cellular expression of these receptors within the CNS, a postulated synergistic antiparkinsonian effect of dual A2A and mGlu5 receptor antagonist warrant further investigation.

P1142
The dopamine stabiliser ACR16 prevents l-DOPA-induced sensitisation in the 6-OHDA-lesioned rat
H. Ponten, A. Carlsson, J. Kullingsjo, C. Sonesson, N. Waters, J. Tedroff (Gothenburg)

Objective: To evaluate the effects of the novel dopamine stabiliser on l-DOPA-induced behavioural sensitisation in the rat 6-hydroxydopamine hemi lesion model. Background: Dopamine stabilisers are compounds representing a new therapeutic concept; with potential to improve the treatment of several CNS disorders exhibiting perturbed dopaminergic function. Long-term treatment of Parkinson’s disease with l-DOPA is compromised by side effects such as dyskinesias and dystonias. Sensitisation, that is, the successive augmentation of locomotor response following repeated dopaminomimetic treatment, is probably an important phenomenon underlying these drug-induced side effects. The present study investigates the effects of ACR16, a novel dopamine stabiliser, on behavioural traits induced by l-DOPA in the rat 6-hydroxydopamine hemi lesion model.

Methods: The effects on motor behaviour after 21 days, twice daily sc injection of either l-DOPA (6.5 mg/kg + decarboxylase inhibitor), l-DOPA + ACR16 (25 μmol/kg) or vehicle, were studied in the rat 6-hydroxydopamine hemi lesion model. Behaviour was recorded automatically in motility-meter boxes.

Results: Repeated twice-daily treatment with l-DOPA (and decarboxylase inhibitor) induced a marked increase in basal locomotor activity and contralateral rotations, reaching maximum after 14 days of treatment. ACR16 co-treatment abolished this augmentation of rotational behaviour, but permitted basal locomotor-activating effects of l-DOPA in the animals.

Conclusion: The results predict a therapeutic role for ACR16 in reducing unwanted consequences induced by repeated l-DOPA administration.

P1143
The diagnosis and management of pergolide-induced fibrosis
P. Agarwal, S. Fahn, S.J. Frucht (Denver, Colorado, USA; New York, New York, USA)

Objective: To report two patients who developed pleural and retroperitoneal fibrosis during treatment with pergolide. Based on our experience and a review of published cases of pergolide-induced fibrosis, we propose guidelines for the diagnosis and management of this rare complication.

Background: The ergot dopamine agonist pergolide mesylate is most commonly prescribed to treat Parkinson’s disease (PD) and restless leg syndrome (RLS). It may rarely induce fibrosis affecting the pleural, retroperitoneal and cardiac valvular structures.

Methods: Case reports and Medline search using key words “pergolide” and “fibrosis” of the English language literature.

Results: Case 1: A 65-year-old man presented at age 54 with PD and was treated with pergolide 7.5 mg/day. Eight years later he developed cough and dyspnea. An MRI of the chest revealed a mass in the left lung, and a needle biopsy was suggestive of non-specific inflammation. He also developed severe bilateral leg edema and dysuria. His erythrocyte sedimentation rate (ESR) was 100 mm/hr. A CT scan of the abdomen was consistent with retroperitoneal fibrosis. A retrograde pyleogram showed bilateral ureteral strictures, and ureteral stents were placed. He was treated with prednisone 60 mg/day for 6 weeks with dramatic improvement.

Case 2: A 71-year-old man with RLS was treated with pergolide which was increased to 5 mg/day. Two years later he developed dyspnea. A chest radiograph revealed a left lobar mass, biopsy of which revealed chronic inflammation and interstitial fibrosis. Pergolide was stopped and dyspnea gradually resolved.

Review of published cases: Eleven papers reported twenty-one patients who developed symptomatic fibrosis during treatment with pergolide. The most common presenting symptom was dyspnea (13/23 patients). Unilateral or bilateral leg edema, cough and chest pain were also seen. The dosage of
pergolide ranged from 1–8 mg/day, and duration of exposure from 1–8 years. The maximum time to diagnosis was 36 months. In six patients the ESR rate was elevated, from 40–127 mm/hr. Chest radiographs were abnormal in most patients with pulmonary fibrosis. Abdominal CT scan was abnormal in those with retroperitoneal fibrosis. Most patients required an invasive procedure to secure the diagnosis. Pergolide was discontinued in all cases. Four patients were treated with steroids with dramatic benefit. Pericardiectomy and ureteral stenting were necessary in some cases. Three patients did not improve despite discontinuation of the drug.

Conclusion: Pergolide can induce fibrosis after relatively brief exposure at low dose. Delay in diagnosis suggests a lack of awareness of serosal fibrosis as a potential adverse event. The non-ergot dopamine agonists pramipexole and ropinirole may be better choices than pergolide for initial first-line therapy. Pergolide should be avoided in patients with elevated ESR, abnormal renal function or valvular heart disease. Patients who develop new dyspnea, chest pain, weight gain or dysuria should undergo echocardiography and CT scan of the chest, abdomen and pelvis to rule out fibrosis. An elevated ESR may be an early marker for this syndrome. Prednisone should be tried in all patients with pergolide-related fibrosis.

P1144
Effects of gap junction blockade in the MPTP-lesioned primate and rodent models of L-DOPA-induced dyskinesia
J. Lee, J. Gomez-Ramirez, T. Johnston, P. Carlen, A.E. Lang, J.M. Brotchie (Toronto, Canada)

Objective: To determine the potential effects of blocking gap-junction communication (GJC) on established t-DOPA-induced dyskinesia (LID) and the development of LID following de novo t-DOPA therapy in Parkinson’s disease.

Background: Gap junctions are macromolecular complexes of connexins that mediate direct electrical and other, cell–cell communication. Striatal GJC is regulated by dopamine and is increased by glutamate transmission, enhancement of which is a key component of pathophysiology of LID. We hypothesised that enhanced GJC plays an important role in the neural mechanisms underlying LID. Here we employ, the gap junction blocker, carbamoxolone (CBX), to address whether GJC is important for the establishment of development of LID.

Methods: Established LID: Rats were lesioned with 6-OHDA in the medial forebrain bundle. Commencing 4 weeks post-lesion, rats received twice daily injections of L-DOPA methyl ester and benserazide (15 and 3.5 mg/kg i.p) for 21 days to establish sensitisation of the net contraversive rotations (NCR) to t-DOPA. The effects of subsequent challenge of CBX (35 mg/kg) on this established sensitisation were assessed. In the monoamine-depleted rat (reserpine, 4 mg/kg, s.c.), t-DOPA methyl ester and benserazide (125 and 50 mg/kg i.p) were administered and seven parameters of locomotion were measured using an automated movement detection system. The effect of CBX (10, 35 or 100 mg/kg) on this activity was assessed. Marmosets (Callithrix jacchus) were rendered parkinsonian with MPTP (2 mg/kg, 5 days, s.c). Following stabilisation of parkinsonism (18 weeks post-treatment), LID was established by twice daily administration of t-DOPA (as Protopa dispersible, 12.5 mg/kg t-DOPA, p.o.) for 3 weeks. The effects of CBX (10 mg/kg s.c) on LID elicited by acute challenge with t-DOPA methyl ester and benserazide (10 and 2.5 mg/kg s.c.) were assessed by a neurologist blinded to the treatment given. Development of LID: 6-OHDA lesioned rats were treated twice daily for 15 days with t-DOPA methyl ester and benserazide (15 mg/kg and 3.5 mg/kg i.p) in combination with either vehicle or CBX (10 or 35 mg/kg). NCR was measured on days 1, 4, 7, 10 and 15.

Results: CBX administered in combination with t-DOPA had no significant effect on established LID in the MPTP-lesioned primate, on established rotational response to t-DOPA in the 6-OHDA rat, or on high-dose t-DOPA induced hyperactivity in the monoamine-depleted rat. In contrast, CBX reduced the development of sensitisation to t-DOPA following de novo administration in the 6-OHDA rat. On day 1, t-DOPA elicited 196 ± 105 NCR/3 hr. Following repeated administration, this effect increased so that on day 15, it was 2,647 ± 638 NCR/3 hr. Co-administration of CBX (35 mg/kg) with t-DOPA significantly reduced this sensitisation (1,224 ± 260 NCR/3 hr) (P < 0.05) on day 15.

Conclusion: Blockade of GJC by agents such as CBX, that do not show selectivity for subtypes of connexins, are unlikely, at the doses given here, to be of benefit in reducing established LID. In contrast, blockade of GJC may be useful as adjunct to de novo t-DOPA therapy as an approach to reduce the development of LID.

P1145
Treatment of restless legs syndrome with subcutaneous apomorphine in a patient with short bowel syndrome
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Background: Restless legs syndrome (RLS) is characterised by dysaesthesias of the legs associated with an urge to move which occur exclusively at rest and can be ameliorated by walking. There are numerous effective drugs for symptomatic treatment of RLS and most of them require oral application. Therefore treatment of a patient not responding to oral medication because of malabsorption is a therapeutic challenge for the clinician.

Case Report: A 38-year old female patient with terminal renal failure was admitted to our neurological clinic with an uncontrollable exacerbation of uremic RLS. The patient also suffered from severe malabsorption following a total colectomy for familial polyposis coli and a subtotal resection of the small intestine because of postoperative adhesions. Her RLS symptoms gradually increased in spite of regular haemodialysis treatment and administration of erythropoietine. Symptomatic treatment with oral medication (levodopa/benserazide up to 300/75 mg, lorazepam up to 2.5 mg, and diazepam up to 20 mg) did not have any effect. Parenteral treatment with the opioid fentanyl as a transdermal patch led to a reduction of symptoms, but its therapeutic efficacy wore off in the course of several months. We therefore introduced subcutaneous injections of the potent dopamine-D1/D2 receptor agonist apomorphine. The initial dose of 0.5 mg did not have a sufficient therapeutic effect but with 1 mg at night time and before each haemodialysis session, the patient experienced a marked reduction of symptoms, which was reflected by a drop of the severity score on the International Restless Legs Syndrome Rating Scale (IRLRS) from 37-20. At a 6 months follow-up, she is still stable on this medication.

Discussion: There are two previous reports of the treatment of RLS with apomorphine. Reuter and colleagues [1999] gave subcutaneous apomorphine infusion to two patients with RLS and found a reduction of nocturnal discomfort, reduced leg movements and improved pain scores. Haba-Rubio and colleagues [2003] investigated the effects of 0.5 mg subcutaneous apomorphine at bedtime on the frequency of periodic limb movements during sleep (PLMS) in nine patients and found a marked reduction of PLMS during the first 4 hr post injection. In the patient we describe here, 1 mg apomorphine at night time and before haemodialysis led to a marked reduction of symptoms as assessed with the IRLSRS.

Conclusion: This case report suggests that subcutaneous apomorphine may be beneficial for patients with RLS who do not respond to oral medication. It further illustrates that opioid patches may also be effective. Once transdermally applied dopamine agonists become available for routine patient care, they may become another line of effective treatment for RLS in patients with malabsorption.

References
Effect of zolpidem on parkinsonian symptoms in patients with advanced Parkinson’s disease

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Objective: To describe the effects of zolpidem in parkinsonian symptoms in patients with Parkinson’s disease.

Background: Zolpidem is a commonly prescribed medication for the short-term treatment of insomnia. Although it is chemically unrelated to benzodiazepines, its action depends on the activation of the benzodiazepine receptor of the GABA-chloride channel. Several patients with Parkinson’s disease have described a significant improvement of parkinsonian symptoms after the administration of zolpidem. In this study, we sought to investigate the parameters related to this unexpected action of zolpidem.

Methods: Fourteen patients with Parkinson’s disease that are currently followed at the movement disorders clinic and receive zolpidem were identified. These patients were asked during the regular visit about the effect of zolpidem on parkinsonian symptoms. In the patients that responded positively, this effect was evaluated objectively with and without levodopa and was compared to the effect of a short-acting benzodiazepine (temazepam).

Results: Five patients reported a significant benefit from zolpidem (mean age = 62 ± 10). All patients had advanced Parkinson’s disease (mean disease duration 17 ± 3.5) and reported both serious fluctuations and dyskinesias. The administration of zolpidem during ‘off’ period produced a sustained improvement of more than 10 points in the UPDRS motor score; an even bigger benefit (≥17 points) was observed during ‘on’ period. Axial symptoms were particularly improved. No effect was observed after the administration of temazepam.

Conclusion: Zolpidem seems to have a robust effect on parkinsonian symptoms, at least in a subgroup of patients suffering from advanced Parkinson’s disease. Moreover, it may show an interaction with dopamine, an effect that is also observed in other brain areas (1). The effect of zolpidem on parkinsonian symptoms is not shared by benzodiazepines and may be related to the fact that zolpidem selectively activates a specific subtype of the benzodiazepine (BZ) receptor; this subtype (type 1 BZ receptor) is abundant in basal ganglia nuclei that are overactive in Parkinson’s disease (i.e., substantia nigra pars reticulata, globus pallidus, and subthalamic nucleus (2)). It could be hypothesized that the selective activation of BZ receptor from benzodiazepines raises significant theoretical issues. References

FIG. 1 (P1146).

P1147

Effect of zolpidem on parkinsonian symptoms in patients with advanced Parkinson’s disease

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Objective: To develop and characterise a novel rat behaviour assay to rapidly screen and identify drugs with potential in the treatment of L-DOPA-induced dyskinesia (LID) in Parkinson’s disease (PD).

Background: LID is a major factor in reducing the long-term usefulness of L-DOPA therapy in PD. To date, the only pharmacological approach to LID available clinically is amantadine, which, maybe poorly tolerated and may lack efficacy in many patients, thereby highlighting the need for further means of controlling LID. While existing animal models of Parkinson’s disease with LID play a crucial role in defining new therapies, they are often costly, time-consuming and require specialized facilities thereby creating a ‘bottleneck’ in the process of drug development for LID. An assay that would allow the rapid identification of drugs with potential therapeutic value in LID could greatly increase the rate at which novel leads were generated, optimised and prioritised and, thus, define which drugs should be assessed in the MPTP-lesioned non-human primate, the best animal model available for subsequent progression into trials in people with LID.
Methods: Male rats (250 g) were rendered akinetic with reserpine (4 mg/kg s.c.). Eighteen hours later, vertical and horizontal locomotor parameters were assessed using an automated movement detection system (Linton, UK). Immediately prior to assessment, rats were injected with a combination of 1-DOPA (50–150 mg/kg i.p.) and benserazide (50 mg/kg, i.p.) in addition to either vehicle, idazoxan (3 mg/kg, i.p.), haloperidol (1 mg/kg, i.p.), amantadine (0.3 mg/kg i.p.) or MK-801 (0.05–0.5 mg/kg i.p.). Behaviours were then assessed for a total of 4 hr. Data for each of the parameters were cumulated into 10-min periods and analysed using one-way analysis of variance (ANOVA), with treatment as the factor and Dunnett’s post hoc test when appropriate. In all cases, \( P < 0.05 \) was taken to represent a significant difference.

Results: Administration of progressively higher doses of 1-DOPA (50–150 mg/kg) to reserpine-treated rats caused a hyperkinetic behaviour characterised by extensive horizontal and vertical activity. Co-administration of 1-DOPA (125 mg/kg) and benserazide (50 mg/kg) with either amantadine (0.3 mg/kg), idazoxan (3 mg/kg) or MK-801 (0.05 mg/kg) reduced vertical activity by 51%, 83% and 90% respectively, while neither drug had significant effects on horizontal activity. In contrast, co-administration of haloperidol (1 mg/kg) reduced both parameters by 72% and 98% respectively.

Conclusion: By demonstrating the ability to discriminate between agents shown previously in MPTP primates to possess anti-dyskinetic properties without compromising anti-parkinsonian efficacy (idazoxan, amantadine and MK-801) from those that do not (haloperidol), this assay may represent an ideal platform for screening analogues and other membrane-agonist antagonists such as 1-DOPA/1-DOPA-induced motor complications.
pain were enrolled in this cross-over double blind, placebo-controlled study. For 7 weeks each patient was treated randomly with placebo and another 7 weeks with controlled release levodopa/carbidopa preparation (200/50 mg dose) with a withdrawal phase of any drug intake of another 4 weeks between both treatment periods. The clinical response to the treatment was evaluated using the visual analogue scale (VAS), the neck pain disability score and patients diary card with the data about sleeping time, hours per day with neck and shoulder pain and additional drug intake. Four times the patients got a total neurological examination with special interest on pain and unilateral shoulder elevation.

Results: A total of 27 of 30 patients (14 male, 16 female, age: 45.03 ± 11.4 years) completed the study. Fourteen of 27 of the patients had during the levodopa intake a significant either total or partial relief of the neck pain in comparison to 627 of the patients during the placebo phase, who had all only a partial relief up to 30% in the VAS (P < 0.05). Furthermore we found a significant decrease in the daily hours with neck pain, local pain maximum rated with the VAS and days with additional drug intake (all: P < 0.05). 1/3 of the patients did not notice a significant improvement by levodopa intake; Only 3/27 of the patients complained about side effects (two patients: nausea, one patient: unpleasant taste of food).

Conclusion: We could show for the first time that levodopa is a very effective treatment in >50% of patients with chronic neck pain and unilateral shoulder elevation. Levodopa should be considered as reliable therapy option for these patients. Interesting parallels between dystonia and chronic neck pain, especially in young patients, should be elucidated in further studies.

[*This study is dedicated to our former head of the department G. Becker, who died at age 42 in a sports accident.*]

**P1152**

**Subcellular re-distribution of the synapse-associated proteins, PSD95 and SAP97 in animal models of Parkinson's disease and L-DOPA-induced dyskinesia**

**J.E. Nash, J. Gomez-Ramirez, G.L. Collinge, C.C. Garner, J.M. Brotchie (Toronto, Canada; Bristol, UK; Stanford, California, USA)**

**Objective:** To determine whether changes in subcellular distribution and expression of synapse-associated proteins (SAPs) may accompany altered striatal neurotransmission in parkinsonism and L-DOPA-induced dyskinesia (LID's).

**Background:** Abnormalities in cell signaling in the striatum play a key role in parkinsonism and LID. SAPs, e.g. PSD95 and SAP97 organise the molecular architecture of synapses, balancing levels of signalling between receptors and signalling molecules. SAPs also play a role in the trafficking of receptors between the synaptic membrane and intrasynaptic structures. Here we assess the levels and subcellular distribution of PSD95 and SAP97 in the 6-OHDA-lesioned rat model of PD and LID.

**Methods:** 6-Hydroxydopamine.HBr (6-0HDA) (12.5 µg) was injected unilaterally into the medullar forebrain bundle. Repeated t-DOPA (6.5 mg/kg administered as methylester with benserazide.HCl (1.125 mg/kg) twice daily, 21 days i.p.) or vehicle was administered, commencing 3 weeks post-lesion, and behaviour was assessed on days 1, 7, 14 and 21. The expression and subcellular distribution of striatal SAP95 and PSD95 were determined using in situ hybridisation, biochemical sub-fractionation, SDS-PAGE, and Western blotting.

**Results:** t-DOPA induced a rotational response, which was enhanced with repeated treatment (758 ± 114 contraversive rotations/hr on day 21, compared to −158 ± 7.3 contraversive rotations/hr on day one). Such behaviour has been characterised as a model for t-DOPA-induced dyskinesia. Following dopamine-depletion, total levels of striatal PSD95 and SAP97 were reduced (25.6 ± 9.9% and 19.0 ± 5.0% of contralateral unlesioned side respectively P < 0.001). The remaining PSD95 and SAP97 was redistributed from the synapse into vesicular compartments. Following repeated t-DOPA treatment, both PSD95 and SAP97 were increased (367.4 ± 43.2% and 159.9 ± 9.5% of control values respectively P < 0.001), and both proteins were redistributed towards synaptic membranes from vesicular compartments. In situ hybridisation showed that changes in PSD95, but not SAP97 were accompanied by similar changes in mRNA.

**Conclusion:** Since PSD95 and SAP97 appear to be involved in the regulation of cellular localisation of receptors at synapses, these data highlight the potential role of abnormalities in the subcellular distribution of synaptic proteins in the pathophysiology of PD and LID.

**P1153**

**The effects of NMDA receptor antagonism in a rat model of tardive dyskinesia**

**C. Tsironis, D. Kiorotsis, A. Evangelou, S. Konitsiotis**

**Objective:** To evaluate the acute effects on orofacial dyskinesia, of two different NMDA receptor antagonists: amantadine, an open channel blocker of the NMDA-receptor channel, and ifenprodil, a non-competitive allosteric (polyamine) site inhibitor.

**Background:** Tardive dyskinesia (TD) is a syndrome that results after chronic treatment with dopamine receptor antagonists. The pathophysiology of this disabling and potentially irreversible movement disorder is still obscure. NMDA antagonists are known to ameliorate dyskinesia in various animal models and in patients with similar hyperkinetic movement disorders, such as levodopa-induced dyskinesia and Huntington’s chorea. Also there is limited evidence form studies in patients with tardive dyskinesia that amantadine may have beneficial effects in this disorder. Therefore, a pathologically increased glutamatergic activity within the basal ganglia could be a possible mechanism underlying these disorders including TD. A widely accepted animal model of TD has been developed, in which a syndrome of orofacial dyskinesia, is induced in rats by long-term neuroleptic administration. Abnormal oral movements appear mainly as vacuous chewing movements (VCMs), but also as tongue protrusions and jaw tremor.

**Methods:** Twelve male Wistar rats weighing 260–380 g were used. For the induction of vacuous chewing movements, the animals received daily injections of haloperidol (1.5 mg/kg, i.p.) for a period of 21 days. Then rats were injected with haloperidol decanoate (38 mg/kg i.m.), every 4 weeks for a total of six injections, resulting in approximately 23 weeks of total haloperidol exposure.

**Results:** Chronic haloperidol treatment significantly induced vacuous chewing movements, tongue protrusions and jaw tremor in rats. Both amantadine (10, 20 and 40 mg/kg), and ifenprodil (5, 10 and 15 mg/kg), reduced haloperidol-induced vacuous chewing movements in a dose-dependent manner. Ifenprodil was found to be more potent in reducing vacuous chewing movements than amantadine, with a ceiling effect at 10 mg/kg. Haloperidol treatment also produced significant tongue protrusions and jaw tremor in rats. Both amantadine and ifenprodil dose-dependently reduced tongue protrusions and jaw tremor and again ifenprodil was found to be more potent in reducing tongue protrusions. Amantadine however in the higher doses produced significant side effects (ataxia, limb dystonia), while ifenprodil had a much more favorable side effect profile. Conclusion: NMDA receptor hypersensitivity might play a significant role in the pathophysiology of tardive dyskinesia, and selective NMDA receptor antagonists can be exploited as novel therapeutic agents for the treatment and prevention of tardive dyskinesia. NMDA antagonists with selectivity for certain sites and/or subunit composition of the receptor may prove safer and more effective compounds for the treatment of this disorder and deserve further testing.

**P1154**

**Tetrabenazine treatment in hyperkinetic movement disorders**

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**Background:** Tetrabenazine (TBZ) is a cathecolamine depletor used for the treatment of a variety of movement disorders. Objective: Our purpose was to assess the efficacy of TBZ in a retrospective chart review in 3 tertiary care movement disorders centers over long term treatment. Patients and Methods: Of 150 patients who were prescribed TBZ 118 were followed up for a total of six injections, resulting in approximately 23 weeks of total haloperidol exposure.

Results: Chronic haloperidol treatment significantly induced vacuous chewing movements, tongue protrusions and jaw tremor in rats. Both amantadine (10, 20 and 40 mg/kg), and ifenprodil (5, 10 and 15 mg/kg), reduced haloperidol-induced vacuous chewing movements in a dose-dependent manner. Ifenprodil was found to be more potent in reducing vacuous chewing movements than amantadine, with a ceiling effect at 10 mg/kg. Haloperidol treatment also produced significant tongue protrusions and jaw tremor in rats. Both amantadine and ifenprodil dose-dependently reduced tongue protrusions and jaw tremor and again ifenprodil was found to be more potent in reducing tongue protrusions. Amantadine however in the higher doses produced significant side effects (ataxia, limb dystonia), while ifenprodil had a much more favorable side effect profile. Conclusion: NMDA receptor hypersensitivity might play a significant role in the pathophysiology of tardive dyskinesia, and selective NMDA receptor antagonists can be exploited as novel therapeutic agents for the treatment and prevention of tardive dyskinesia. NMDA antagonists with selectivity for certain sites and/or subunit composition of the receptor may prove safer and more effective compounds for the treatment of this disorder and deserve further testing.
to +3) a composite grade from patient and care-giver, scale over variable periods of time. Patients had variety of hyperkinetic movement disorders including: dystonia (generalized, and focal: axial, Meige syndrome, torticollis, blepharospasm, bruxism), Huntington’s disease (HD) or other choreas, tardive dyskinesia (TD) or akathisia and Tourette syndrome.

Results: Patients mean age was 48.8 ± 18.7 years, 48 men (40.7%) with a mean disease duration of 93 months. The mean follow up time was 22 months and the mean TBZ dose was 76.2 ± 22.5 mg/day (median 75 mg, range: 25–175 mg/day). The mean CGIC score was +1 (mild improvement). The group of patients who scored +3 on the CGIC (very good improvement) represented (N = 22, 18.6%) of all patients. They suffered from HD or other types of chorea (N = 9, 7.6%), facial dystonia/dyskinesia (N = 7, 5.9%), one with TD, two with trunk dystonia, two patients had Tourette syndrome and one suffered from tardive akathisia. This group had the longest treatment durations (mean: 25.4 ± 21.3 months) and received a mean dose of 70.5 mg/day (median 75 mg/day).

Conclusion: We conclude that TBZ is a moderately effective treatment for a large variety of hyperkinetic movement disorders, with excellent effects in a subgroup with chorea and facial dystonias/dyskinesias.

P1155
Three cases of peripheral edema caused by prolonged use of ropinirole
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Objective: To describe characteristic of peripheral edema (PE) in 3 Parkinson’s disease (PD) patients who had been treated with ropinirole.

Background: Ropinirole is a newer dopaminergic agonist, which has been shown to be an effective treatment for early and advanced PD. It is a potent nonergoline dopaminergic agonist that binds specifically to D2-like receptors with a selectivity similar to that of dopamine (D3>D2>D4). There are reports of PE with other dopaminergic agonists, but peripheral edema had been rarely reported with the use of ropinirole.

Methods: We describe clinical characteristic of PE in 3 patients who had been chronically treated with ropinirole. Occurrence of edema was dose dependent and complete resolution of edema followed discontinuation of ropinirole. In all cases other medical causes of edema had been excluded and medical therapy to treat edema failed.

Results: First patient had 15-year history of PD and had been treated with ropinirole, amantadine and trihexyphenidyl. Severe generalized edema affecting both upper and lower extremities, trunk and face developed when the dose of ropinirole was increased from 6–24 mg a day. The edema, which had been present for 2 years, resolved completely after discontinuation of ropinirole. Addition of pramipexole several months later caused reoccurrence of milder form of PE affecting extremities and trunk. The second patient had 12-year history of PD and therapy consisted of 1,450 mg of levodopa and 24 mg of ropinirole daily. Asymmetrical lower extremity edema developed when the levodopa dose was increased to 1,600 mg per day. After discontinuation of ropinirole and lowering the dose of levodopa to 1,450 mg daily, patient had complete resolution of edema. The addition of pramipexole did not cause recurrence of symptoms. Third patient had 8-month history of PD and developed asymmetrical lower extremity edema when the dose of ropinirole had reached 8 mg per day. Discontinuation of ropinirole produced complete resolution of edema.

Conclusion: We report 3 patients with peripheral edema that was attributable to ropinirole therapy. All 3 patients had been on medication with ropinirole for extended period of time, and medical causes had been excluded. The clinical spectrum varied from asymmetrical lower extremity edema to generalized severe edema with erythema. Edema occurred months after therapy initiation, was dose dependent, misdiagnosed in all 3 cases and resistant to medical therapy with diuretics and antihistamines.

Discontinuation of ropinirole produced complete resolution of edema. Initiation of another dopaminergic agonist should be done cautiously as reoccurrence of symptoms was observed in one patient. Clinicians should be aware of this side effect of ropinirole as early recognition could save unnecessary medical workup and treatment.

P1156
A high-throughput screening assay for identifying potential neuroprotective agents in Parkinson’s disease
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Objective: To develop and characterize a high throughput assay, which allows rapid screening of potential neuroprotective drugs in Parkinson’s disease.

Background: The potential benefits of identifying neuroprotective agents for Parkinson’s disease (PD) are clear. Unfortunately, current methods for screening novel neuroprotective agents are prolonged and incomplete. In particular, in the absence of a single cause of PD and of agents with proven neuroprotective properties in man, it is impossible to define the validity of a model in which to screen novel agents. Here, we define an assay, which combines ease of use, reproducibility, and applicability to high throughput screening in a way that recapitulates many aspects of the known mechanisms of cell death in PD. This cell assay, the neuroprotective potential of compounds to be profiled in a variety of different states of metabolic and/or oxidative stress, protosom dysfunction, all of which have been linked with familial or sporadic PD. Thus, this assay accounts for the fact that several mechanisms may be responsible for dopamine cell death and is not constrained by a specific mechanistic hypothesis.

Methods: A dopaminergic neurobastoma cell line (SH-SY5Y) in combination with a redox-sensitive dye (Alamar Blue) was used to measure cell viability. Viability was assessed in the presence of compounds, which have previously been shown to be neuroprotective in different models of Parkinson’s disease, or to interfere with processes proposed as being relevant to neurodegeneration in PD. The protocol has been optimized for application in 96 and 384 well plates with an automated fluorescence plate reader.

Results: Several classes of compound, previously shown in animal models of PD to cause a dose-dependent increase in cell death, resulted in almost complete (>95%) cell loss at the highest concentrations used. The proteosome inhibitor, Z-Ilc-Glu(Obu)-Ala-Leu-H (PS1) decreased cell viability after 48 hr of incubation, with an IC50 = 3 uM. In contrast, 6-hydroxydopamine and dopamine were more potent, and decreased viability more rapidly (IC50 = 0.3 uM after 24 hr). In addition, compounds that have previously suggested as being neuroprotective (e.g., NMDA receptor antagonists, monoamine oxidase B (MAO-B) inhibitors prevented dopamine-induced decreases in cell viability in this assay. Dopamine (600 uM) alone resulted in an 80 ± 7.4% decrease in cell viability, which was completely blocked by the MAO-B inhibitor, pargyline (0.001–100 uM). Furthermore, NMDA receptor antagonists MK-801 and APV increased cell viability by 39.6 ± 11.3% and 36.1 ± 12.1% respectively in the presence dopamine (600 uM).

Conclusion: This assay is a rapid, inexpensive and reproducible screening method for profiling compounds, which may be neuroprotective in PD. The assay is not reliant on a single hypothesis or mechanism of cell death in Parkinson’s disease, but is based on the intrinsic interactions between dopamine metabolism and other metabolic stressors, which may contribute to differing levels between patients with PD. Promising neuroprotective agents revealed with this assay will be tested in animal models of Parkinson’s disease.

P1157
Continuous stimulation: Supplementation of levodopa/carbidopa with entacapone reduces movement fluctuations
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There is growing evidence that continuous dopaminergic stimulation prevents onset of motor fluctuations and dyskinesia in patients with Parkinson’s disease (PD). Therefore, the short plasma half life of levodopa/dopadecarboxylase inhibitor [LD/DDI] preparations contribute to onset of these motor complications in the long-term. A possible strategy to prolong plasma metabolism is the addition of a COMT inhibitor, i.e., entacapone [EN]. Objectives of this trial were to evaluate (1) the clinical response to this increase of dopaminergic substitution due to EN supplementation and (2) the intensity of fluctuations of motor behaviour. We used peg insertion
with a computer based device [Muller et al., CNS 2000;27:311–315] and UPDRS III scoring for assessment of motor function in not optimum titrated PD patients, who were treated with LD/Carbidopa [LD/CD] (t.i.d., 50–150 mg) on day 1 and with the corresponding Levodopa/Carbidopa/Entacapone [Stalevo®] (t.i.d., 50–150 mg) on day 2 within a standardized setting. The additional antiparkinsonian drug treatment remained stable. We scored patients [N = 6; age: mean = 61.5 SD = 11.1, range 39–75 years; 5 men, 1 woman] on both investigation days 8 times with the UPDRS III and performed the instrumental task within 8 hours at fixed, identical timepoints. We computed the differences to baseline on each day (baseline − assessment timepoint 1.2 etc.) in order to calculate the movement fluctuations. We used MANCOVA with age as covariate for statistical analysis. UPDRS III significantly reduced [day 1: mean = 24.9 SD = 8.7, 10–41; day 2: mean = 23.4 SD = 7.7, 8–35; F(df 2, df 35) = 7.8; P = 0.007]. Peg insertion [sum of right and left hand; day 1: mean = 124.3 SD = 14.6, 99.9–155.8; day 2: mean = 110.5 SD = 13.6, 87.5–134.5 (sec); F(df 2, df 47) = 114.7; P = 3.32E-14]. Changes of computed differences of UPDRS III scores [day 1: mean = 5.7 SD = 5.6, −8–14; day 2: mean = 3.2 SD = 4.8, −11–11.5; F(df 2, df 35) = 14.7; P = 0.0005] and peg insertion intervals significantly reduced. No impact of age appeared. Both rating outcomes and peg insertion results show that switch from LD/CD to Stalevo significantly reduced. No impact of age appeared. Both rating outcomes

P1159

Effect of (−)-BPA on the expression of neurotrophins and their receptors in mesencephalic slice cultures

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Objective: The effects of (−)-BPA on the synthesis of BDNF and the transcription of BDNF, NT-3, TrkB and p75 were assessed using rat mesencephalic slice culture.

Background: R(+)-1-(Benzo[4,5]furan-2-yl)-2-propylaminopentane [(−)-BPA] enhances electric field stimulation-induced release of catecholamine from isolated rat brainstem, and improves motor deficits in animal models of Parkinson’s disease. Thus, (−)-BPA is considered as a candidate of antiparkinsonian agent. On the other hand, (−)-BPA has been reported to upregulate the synthesis of neurotrophins in cultured astrocytes. Neurotrophins, such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are well known to affect the survival and differentiation of neurons.

Methods: (−)-BPA (10−7–10−11 M) was applied in mesencephalic slice culture (10 DIV) prepared from Wistar rats (P3) for 48 hr. BDNF content was analyzed by ELISA method. The mRNA expressions of BDNF, NT-3, and their receptor TrkB and p75 were analyzed by semi-quantitative RT-PCR.

Results: (−)-BPA significantly increased BDNF content and the mRNA expression. Furthermore, (−)-BPA increased TrkB mRNA. But (−)-BPA did not increase NT-3 and p75 mRNA.

Conclusion: (−)-BPA-induced upregulation of BDNF may be useful to maintain mesencephalic neurons, suggesting a usefulness of (−)-BPA in the treatment of progressive neurodegenerative disorders such as Parkinson’s disease.

P1160

Double blind evaluation of symptomatic effect at the end of a 12-week treatment with safinamide, a new neuroprotectant

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Background: Neuroprotection is the new frontier in treating PD. A major issue in neuroprotection studies is how to segregate true neuroprotection from a symptomatic effect. Safinamide is a new neuroprotectant with additional symptomatic efficacy due to MAO-B and dopamine uptake inhibition.

Methods: At termination of a 12-week treatment with two doses of Safinamide [0.05 mg/kg/day (maximal MAO-B-I) and 1.0 mg/kg/day (implying the other mechanisms)] 24 patients had their UPDRS/III scores re-evaluated in double blind after at least 2 week treatment withdrawal. Results: In this subgroup of patients during the 12 week study there had been a mean percent improvement of 23.5, 45.7 and 36.5 in the placebo, lower and higher dose groups respectively. No AEs were recorded during withdrawal. UPDRS/III scores reverted close to the one recorded at baseline (pre-12 week study) with a mean value of 8.4, 0.09 and 5.9% less than baseline for the placebo, lower and higher dose respectively. As for the main study, statistical evaluation with the Kruskal-Wallis test showed the difference to be significant for the 1.0 mg/kg/day dose compared to placebo (P < 0.005).

Conclusion: This study indicates that the observed effect in the main study was symptomatic in nature. If confirmed in longer studies, this should be subtracted from the putative neuroprotective action.

P1161

Changes in neuroendocrine response to L-DOPA during long-term treatment in restless legs syndrome augmentation

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Objective: To investigate a possible relation of RLS augmentation to dopamine receptor sensitivity changes during long-term treatment with L-DOPA by means of a neuroendocrine challenge.
Background: RLS augmentation is a common complication of long-term treatment with dopaminergic drugs and reflects an overall worsening of RLS symptoms during treatment. The pathophysiology of RLS augmentation remains unknown. Nevertheless, changes in dopamine receptor sensitivity resulting from long-term dopaminergic treatment have been suggested as a cause.

Methods: Fifteen previously untreated patients with idiopathic RLS were treated for 12–15 months (mean: 14.4 months) with L-DOPA. The mean dosage was 182 mg/day. Severity of symptoms was evaluated every two months by means of the International RLS scale (IRLS). A blind rater evaluated patients regarding presence (AUG) or absence of augmentation (N-AUG). In addition, patients underwent before and after treatment a suggested immobilization test (SIT) followed by a sleep study. On the following day, patients underwent at 23:00 an L-DOPA neuroendoctrine challenge: After insertion of an iv line, 400 mg L-DOPA (+50 mg carbi-DOPA) were administered orally at 2300. Blood was drawn 20 and 5 min before administration of the drug, as well as 15, 30, 45, 60, 75, 105 and 120 min after, and analyzed for plasma values of PRL. A group of 13 age- and gender-matched healthy controls underwent at baseline also the SIT, the sleep study and the neuroendoctrine challenge. Hormonal assays were performed blindly to diagnosis, treatment outcome or augmentation status.

Results: (a) Seven men and eight women were included in the sample, with a mean age of 57.3 years (SD: 2.9). The mean (SD) IRLS-score improved during treatment from 25.4 (3.9) to 12.5 (4.1) points (P < 0.05). Six out of the fifteen patients were classified as AUG. (b) In both RLS and control groups, baseline PRL plasma levels decreased following acute administration of L-DOPA. However, the reduction (measured as area under the curve-AUC) was more pronounced in RLS than in controls (P < 0.05). (c) Following long term dopaminergic treatment, PRL was less inhibited by acute administration of L-DOPA than before treatment, in the AUG group (P < 0.05) but not in the N-AUG group. (d) No statistical differences were found between PRL response to L-DOPA following long term treatment in AUG and controls.

Conclusion: The results suggest a mild decrease in dopamine receptor sensitivity in RLS patients during long term treatment with L-DOPA, particularly for those undergoing augmentation. A loss of therapeutic efficacy due to a reduction in postsynaptic dopamine receptor sensitivity during long-term dopaminergic treatment might mediate RLS augmentation.


Aripiprazole in the treatment of movement disorders

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Background: Aripiprazole is a D2 and 5-HT1A receptor partial agonist and a 5-HT2A receptor antagonist, making it a novel dopamine-serotonin system stabilizer with potential use in movement disorders. We postulated that aripiprazole improves psychosis in Parkinson’s disease (PD) without worsening the motor symptoms of PD and decreases drug-induced movement disorders also. Psychosis (hallucinations and delusions) is a serious late complication of PD, occurring in an estimated 30% of treated patients and a major risk factor for institutionalization and poor outcome. It is postulated that dopamine receptor hypersensitivity, and dopamine induced increase in serotonin release, cause psychosis in treated PD. The former mechanism may cause dyskinesia also. Studies done show aripiprazole to be a D2 and 5-HT1A receptor partial agonist, and a 5-HT2A receptor antagonist which can enable it to act as a stabilizer of the dopamine-serotonin system (1,2). Thus aripiprazole may be useful in the treatment of psychosis and medication induced dyskinesias where other treatments have failed.

Methods: We present our experience in three patients.

Results: (1) An 81-year-old woman with PD for 15 years, on dopaminergic treatment for 8 years, developed psychosis and dyskinesias one year prior to presentation. A decrease in dosage of dopaminergic medications did not help the symptoms. Quetiapine worsened her PD motor symptoms. Aripiprazole 5 mg qd treated her psychosis and decreased her dyskinesias, without worsening her PD symptoms. (2) A 62-year-old man with PD for 7 years, on dopaminergic treatment for 6 years, developed disabling motor fluctuations and psychosis for 1 year prior to presentation. He was started on aripiprazole 10 mg qd with resolution of psychosis, but with worsened PD symptoms, which improved on discontinuation of aripiprazole. (3) A 42-year-old woman with Phenylketonuria, mental retardation and drug-induced tardive dyskinesia and dystonia, did not improve with a medication adjustments. Aripiprazole at 15 mg qd significantly improved her tardive symptoms.

Conclusions: Aripiprazole as a dopamine-serotonin stabilizer has potential use in the treatment of movement disorders.

References

Endocannabinoid levels are altered in parkinsonism and t-DOPA-induced dyskinesia in the MPTP-lesioned macaque

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Objective: To assess the levels of the endocannabinoids 2-arachidonyl glycerol (2-AG) and anandamide (AEA) throughout the basal ganglia in the MPTP-lesioned macaque model of Parkinson’s disease (PD) and t-DOPA-induced dyskinesia (LID).

Background: Endocannabinoids have a diversity of effects, mediated via cannabinoid CB1, vanilloid VR, and other non-receptor mechanisms, that can modulate neuronal and glial signalling within the basal ganglia. It has previously been hypothesised that enhanced levels of endocannabinoids might contribute to (1) mechanisms compensating for loss of dopamine in pre-symptomatic PD, (2) generation of parkinsonian symptoms in PD, (3) generation of LID in PD. Here, we assess the levels of 2-AG and AEA in the striatum, GPs, GPi and SN in the MPTP-lesioned macaque model of PD.

Methods: Twenty-seven female macaques were assigned to 4 groups: 1, normal (n = 6); 2, parkinsonian, untreated (n = 5); 3, parkinsonian, acute t-DOPA, non-dyskinetic (n = 6); and 4, parkinsonian, chronic t-DOPA, dyskinetic (n = 10). Animals in group 1 received only vehicle treatment. Animals in groups 2, 3 and 4 were rendered parkinsonian by repeated daily MPTP administration (0.2 mg/kg/day, for 14–18 days). Following stabilisation of parkinsonism (4 months), group 4 animals received twice daily t-DOPA treatment, tailored to provide maximal anti-parkinsonian benefit in each individual animal, for 6 months and killed 1 hr after their last t-DOPA administration. These animals demonstrated LID characterised by an idiosyncratic mix of chorea and dystonia. Group 3 animals received a single dose of t-DOPA, sufficient to alleviate parkinsonian symptoms, 1 hr prior to being killed. Brain regions were dissected and frozen immediately.

The levels of 2-AG and AEA were assessed by isotope dilution atmospheric pressure chemical ionisation liquid chromatography-mass spectrometry.

Results: AEA, but not 2-AG, was increased in GPe (149 ± 9%; P < 0.001) of parkinsonian, untreated compared to normal animals. Reversal of parkinsonism with acute t-DOPA administration had no significant effect on this rise. On the other hand, the generation of LID was accompanied by reductions of 2-AG in GPe (–37 ± 8%) and AEA in SN (–49 ± 15%) compared to parkinsonian animals.

Conclusion: These data highlight the critical and complex role played by endocannabinoids, especially in GPe, in Parkinson’s disease and LID. Although broadly consistent with rodent data, differences in the identity of endocannabinoids involved in different regions of the basal ganglia and in parkinsonism vs. LID, demonstrate the need for studies in non-human primates with respect to understanding these signalling systems in movement disorders. The data also suggest the multiple opportunities for manipulation of the endocannabinoid system, e.g., with modulators of cannabinoid uptake, synthesis and metabolism as well as the direct modulation of CB1 and VR1 receptors in the treatment of PD and LID.
Involvement of both delta subtypes in the anti-parkinsonian actions of the delta opioid receptor agonist SNC80 in the reserpine-treated rat

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Objective: To define the role of delta subtypes in the anti-parkinsonian actions of delta opioid receptor agonists in the reserpine-treated rat model of Parkinson’s disease.

Background: In both rodent and non-human primate models of Parkinson’s disease (PD), stimulation of delta opioid receptors has profound anti-parkinsonian actions that are equivalent, in efficacy, to dopamine replacement. Two subtypes (delta1 and delta2) of delta opioid receptors exist, and both are found within the basal ganglia. It is unknown which subtypes mediate the anti-parkinsonian actions of non-subtype selective delta opioid receptor agonists. Here, we employ the delta1-selective antagonist 7-benzylenediaminealxetone (BNTX) and the delta2-selective antagonist, 17-(cyclopropylmethyl)-6,7-didehydro-1,3-bis[(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl-N,N-diethylbenzamide (SNC80) to address this issue in order to define whether subtype-selective delta agonists might have therapeutic benefit in PD. Such selectivity might be preferable, as it would be anticipated that a more selective agent could have a less extensive side effect profile and a broader therapeutic window.

Methods: Male Sprague-Dawley rats (250–300 g) were rendered parkinsonian by reserpine administration (3 mg/kg, s.c.). Eighteen hours later, the effects of BNTX (0.3–3 mg/kg i.p) and naltriben (0.03–3 mg/kg i.p) in blocking the anti-parkinsonian actions of (+)-4-[(alphaR)-alpha-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC80) (10 mg/kg i.p) were tested. Five aspects of locomotion, in both the horizontal and vertical plane, were assessed using automated activity monitors (Linton, UK) for 2 hr.

Results: In reserpine-treated rats, SNC80 increased horizontal aspects of locomotion. With respect to total horizontal activity (total over 2 hr) activity in vehicle-treated animals was 399 ± 94 compared to 2187 ± 386 following SNC80 administration (P < 0.001). The actions of SNC80 were completely blocked by the addition of BNTX, total activity being 546 ± 59 and 738 ± 98 for SNC80 combined with 1 and 3 mg/kg BNTX respectively. Similarly, naltriben blocked the actions of SNC80, total activity being 696 ± 106, 596 ± 217 and 451 ± 47 for SNC80 in combination with 0.1, 0.3 and 1 mg/kg naltriben respectively.

Conclusion: Activation of both delta1 and delta2 subtypes of delta opioid receptors is necessary to mediate the anti-parkinsonian actions of delta opioid receptor agonists. Non-subtype selective delta opioid receptor agonists are likely to be more effective anti-parkinsonian agents than subtype selective ones.

Methods: Patients requiring treatment with BTX for CD, with previous good response to BTX were randomized in a double-blind manner into either BTX-A or BTX-B groups. Injection sites and dosage were determined by the treating physician. BTX-B (Myobloc, Elan Pharmaceuticals) dosage was calculated at 50 times the BTX-A (Botox, Allergan Pharmaceuticals) units. In addition to assessments of efficacy, the following measures of autonomic function were assessed at baseline, 2-week and 12-week post-injection: 1. Orthostatic blood pressure (BP) and heart rate (HR) 2. Orthostatic HR regulation (longest R-R after standing, divided by shortest R-R after standing, 3. HR Variation with respiration. 4. Schirmer test for saliva production. 5. Composite Autonomic Scoring Scale (CASS) questionnaire [Suarez et al., 1999]. In addition, ocular autonomic testing consisted of pupillary reaction to light, refraction, amplitude and near point of accommodation, tonometry and the Visual Function Questionnaire (VFQ).

Results: After screening, 20 subjects with CD responsive to BTX-A were randomized and completed the study: BTX-A 11 patients (7 female; 55 ± 12 years old; 228 ± 83 Botox Units); BTX-B: 9 patients (7 female; 64 ± 10 years old; 12083 ± 5899 Myobloc Units).

Saliva production decreased significantly with BTX-B (P < 0.01) with Schirmer tests. This was associated with increased complaints of dry mouth. There was no change in orthostatic R-R interval and no development of orthostatic hypotension. Whereas the BTX-B group had a lower HR variation with respiration, this difference was present before injection and did not change differentially between groups after treatment. On the CASS, dysphagia was present after injection in 2/11 patients treated with BTX-A compared to 5/9 with BTX-B. There was increased severity of constipation in 3/9 BTX-B- but in 0/11 BTX-A-treated patients. Other differences in frequency of reporting of autonomic symptoms were not significant. There was no significant change in either the symptoms of the VFQ or any of the measured ocular variables.

Conclusion: Patients treated for CD with BTX-B develop decreased saliva production, dry mouth and constipation more than those treated with BTX-A. Neither group seemed to develop significant autonomic dysfunction as measured by measures of BP, HR variation or visual function.

Anti-parkinsonian effects of delta opioid receptor stimulation are accompanied by dystonia in MPTP-lesioned non-human primates previously treated with L-DOPA

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Objective: To assess the ability of delta opioid receptor stimulation to alleviate parkinsonian symptoms and elicit dyskinesia in MPTP-lesioned primates previously treated with L-DOPA.

Background: L-DOPA-induced dyskinesia (LID) remains a significant challenge in the treatment of Parkinson’s disease (PD). Non-dopaminergic therapies have attracted great interest in part because they may be associated with less dyskinesia. We have previously shown that stimulation of delta opioid receptors can alleviate parkinsonian symptoms in both rodent and the MPTP-lesioned primate models of PD. These anti-parkinsonian effects are quantitatively and qualitatively similar to those of dopamine replacement therapy (DRT). In MPTP-lesioned primates that had not previously received DRT, delta agonists alleviate parkinsonism without eliciting dyskinesia. However, the vast majority of patients with PD have received DRT and experience some dyskinesia when treated with L-DOPA. The present study was designed to assess the potential of delta agonists to alleviate parkinsonism in L-DOPA-primed MPTP-lesioned primates.

Methods: Marmosets (Callithrix jaccus) were rendered parkinsonian by treatment with MPTP (2 mg/kg, s.c., 5 days). Following stabilisation of parkinsonism (18 weeks), L-DOPA (administered as Prolopa dispersible, 12.5 mg/kg t.DOPA and 3.125 mg/kg benserazide) was administered twice daily in Citosan (p.o.) for 3 weeks to establish stable, reproducible LID. The effects of L-DOPA (administered as methyl ester, s.c.) and of the non-subtype selective delta agonist (+)-(R)-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl-N,N-diethylbenzamide (SNC80) (10 mg/kg, s.c.) on both parkinsonian and in elicits dyskinesia
were assessed by an observer blinded to the treatment given. The effect of selective stimulation of delta_1 and delta_2 opioid receptors was assessed by administration of SNC80 with a delta_2 and delta_1 antagonist respectively, 17-(cyclopropylmethyl)-6,7-didehydro-3,14-dihydroxy-4,5-epoxy-6,7,2’3’-benzo[b]furanomorphinan (naltriben, 0.1 mg/kg) and 7-benzylidenenaltrexone (BNTX, 1 mg/kg).

Results: L-DOPA alleviated parkinsonism and elicited dyskinesia that was characterised by choreic movements in all animals. SNC80 provided rapid alleviation of parkinsonism, within 15 min, to a level equivalent to that of L-DOPA, at peak effect, though with shorter duration. This anti-parkinsonian action was accompanied by marked to severe dyskinesia. The nature of the dyskinesia elicited by SNC80 was predominantly dystonic. SCN80 in combination with naltriben or BNTX did not alleviate parkinsonism nor elicit dyskinesia.

Conclusion: Stimulation of delta opioid receptors has profound anti-parkinsonian effects in the MPTP-lesioned non-human primate. However, in previously primed animals, these are accompanied by dyskinesia. These anti-parkinsonian actions require both delta_1 and delta_2 opioid receptor stimulation. Delta opioid agonists are unlikely to replace dopamine replacement therapy in the treatment of advanced PD but may have value as de novo therapy to delay the need to initiate DRT.