DOWNLOAD PDF UNDERSTANDING PARKINSONS DISEASE MOUSSA B.H. YOUDIM AND PETER RIEDERER

Chapter 1 : Iron, brain ageing and neurodegenerative disorders | Read by QxMD

By Moussa B. H. Youdim and Peter Riederer Tackling Turbulence with Supercomputers Computers only recently became powerful enough to illuminate simple examples of this great classical problem.

As reviewed by Magyar et al , Weinreb et al , Naoi and Maruyama Particular clinical features of the depressive symptom profile in patients with PD have been described Wermuth and Bech, ; Brand et al. Depression in PD is associated with increased disability and reduced quality of life, the impact of depressive symptoms in early PD especially should not be underestimated Ravina et al. MAOIs in depression While early studies suggested that MAOIs were not as effective as other antidepressants, more recent studies have demonstrated that, when prescribed in adequate dosages, phenelzine and tranylcypromine are as effective as other antidepressants Pare, Table 6 gives a summary of important controlled studies with tranylcypromine. In a recent study tranylcypromine, 60 mg daily, was found effective in the treatment of panic disorder and social anxiety disorder comorbidity Nardi et al. Table 6 Randomised, double-blind controlled studies with tranylcypromine TCP in the treatment of depressive disorders from Laux et al. The main indications for the classical irreversible MAOIs are subgroups of depression such as atypical depression, dysthymia or for patients who do not respond to reuptake inhibitors, so-called therapy resistant depressions Nolen et al. The therapeutic efficacy of moclobemide has been assessed in numerous controlled studies comparing it with placebo and established antidepressants for reviews see Laux, ; Fitton et al. An overview of the most relevant trials is given in Table 7. Table 7 Open in a separate window C: Large trials in patients with major depression have generally confirmed that the efficacy of moclobemide is equivalent to that of TCAs beside some negative studies. Subgroup analyses of patients revealed moclobemide to be effective in patients with dysthymia or atypical depression especially Lonnqvist et al. These data are limited and great caution is necessary because of the potential to induce the serotonin syndrome when combining moclobemide with serotoninergic drugs. MAO-B inhibitors like selegiline in high dosage have been used in therapy-refractory depressions probably due to non-selective MAO effects see review Laux, In several controlled studies selegiline transdermal system exhibited significant treatment effects on MDD including core depression symptoms, vegetative symptoms and motor retardation Frampton and Plosker, ; Robinson et al. A combination of selegiline and 5-hydroxytryptophan has been tested in a pilot study and proved antidepressant efficacy Mendlewicz and Youdim, A pharmaco-epidemiological study in Danmark showed that persons treated with antiparkinson drugs have higher frequency of antidepressant drug treatment than have controls Brandt-Christensen et al. Most authors conclude, that recommendations for the optimal drug treatment of depression in PD are difficult to give Burn, Thirty-seven patients with early PD have been treated successfully with tranylcypromine TCP , parkinsonian symptoms improved slightly, follow-up after 1. No other studies have been reported with TCP so far. Ten patients with PD have been treated successfully with moclobemide vs. Sufficient data allowing conclusions are missing. Clinical experience and studies in the last years clearly have shown the necessity of higher dosage of moclobemide pointing out the lack of early sufficient dose-finding studies. Recommended daily doses of phenelzine are 30 to 90 mg, of isocarboxazid 30 to 60 mg, respectively. Dietary restrictions are essential for tranylcypromine tyramine-rich food , unnecessary for moclobemide taken at the end of a meal. A 2 week wash-out period is required for switching between tranylcypromine and other classes of antidepressants, not between moclobemide and other antidepressants. In patients with severe hepatic impairment, tranylcypromine and moclobemide dosages should be reduced by one-third to one-half in such patients Atkinson and Ditman, ; Fitton et al. The mostly limiting factor in the use of these MAOIs is the potential for dangerous interactions with tyramine-rich foods and sympathomimetic and serotoninergic substances. Therefore, prescription is only possible to patients being strongly compliant with dietary restrictions. In the case of RIMAs like moclobemide there is no need for dietary restrictions. For "selegiline transdermal system" tyramine dietary restrictions are not needed. The incidence of the most frequently

reported adverse effects from patients receiving MAOIs are summarised in Table 7. Unlike nonselective, irreversible MAOIs and tricyclics, moclobemide has little effect on the cardiovascular system and lacks anticholinergic properties associated with TCAs Moll et al. In almost all controlled clinical studies comparing moclobemide with TCAs moclobemide showed clearly superior tolerability Versiani et al. Headache, insomnia and agitation were the only one side effects being reported more frequently with moclobemide compared to re-uptake inhibiting antidepressants. Dizziness and nausea have been noticed additionally. No systematic changes in blood pressure were observed with moclobemide, whereas increases in both blood pressure and pulse were recorded for tranylcypromine Laux et al. Body weight gain has been observed with phenelzine and isocarboxazid, no clearcut cases with tranylcypromine or moclobemide have been reported Cantu and Korek, Compared to SSRIs moclobemide showed fewer gastrointestinal adverse effects and sexual dysfunction have not been reported with moclobemide Philipp et al. Regarding cognitive functions data in favour of moclobemide compared to other antidepressants are available: Behavioural toxicity assessed by choice reaction time is very low or missing, psychomotor functions seem not be influenced negatively perhaps even improved Hindmarch et al. The principal side effects of selegiline transdermal were local dermal reactions and dose-related insomnia Robinson and Amsterdam, Several fatal overdoses have been reported when moclobemide was combined with serotoninergic antidepressants like citalopram, clomipramine or fluoxetine due to occurrence of a serotonin syndrome Neuvonen et al. In contrast, irreversible MAOIs like tranylcypromine must be regarded as less safe regarding to the fatal toxicity index Henry et al. Side effects of selegiline and rasagiline Selegiline is well tolerated. Rasagiline Adverse reactions as seen with other dopaminergic drugs, like nausea, vomiting, orthostatic hypotension, somnolence, hallucinations and dyskinesias are tolerable in most cases. Although interactions may be suggested when MAO-B inhibitors are combined with COMT-inhibitors, such adverse reactions have not been reported to be of relevance. The cardiovascular risk in selegiline and rasagiline treated PD Selegiline is metabolized mainly to desmethylselegiline, L-amphetamine and L-metamphetamine. L-Amphetamine has about a ten times lower activity on the peripheral sympathetic system compared to D-amphetamine. On the other hand, both are equipotent in blocking striatal dopamine uptake Coyle and Snyder, A clinical trial of daily 10 mg selegiline vs. Therefore, selegiline is not acting via the amphetamine metabolites. Also, from the side effect profile as reported in the large selegiline based trials there is no evidence for enhanced cardiovascular risk eg. Parkinson Study Group, ; This holds true also when selegiline is compared to treatment based on L-DOPA and dopaminergic receptor agonists. However, head-to head comparison is missing. Nevertheless, to avoid further such discussion a sublingual galenic form of selegiline treatment has been developed named Zydis-selegiline Clarke et al. A reduction of the daily dosis of 10 mg selegiline to 1, 25 mg selegiline is advised. The bioavailability of selegiline when given as "melting-tablet" is more homogene and better reproduceable compared to the peroral type of application Clarke et al. In addition a transdermal galenic form of selegiline has been developed for the treatment of major depression again reducing selegilines first-pass biotransformation Frampton and Plosker, ; Robinson et al. Melting tablet and transdermal selegiline avoid first-pass metabolism, cause higher drug availability in MAO-B preferring organs and reduce the concentration of metabolites. Increased drug concentration may cause significant inhibition of both MAO-B and -A in brain but not in the periphery. This explains selegilines antidepressant activity when combined with 5-hydroxytryptophan without the cheese-effect and without the serotonin syndrome Mendlewicz and Youdim, Under clinical conditions selegiline is not more "toxic" than other dopaminergic treatment strategies. In fact the side effect and adverse reaction profile of selegiline has been evaluated as being well tolerated and "mild" compared to other PD treatment strategies, eg. It should be mentioned that L-amphetamine is in clinical use for the treatment of attention-deficit-hyperactivity syndrome ADHD without major side effects. In line with this are several studies as summarized by Reidenberg showing no abuse liability of selegiline. The contribution of desmethylselegiline DMS to the effects of selegiline has been underestimated so far. This is in agreement with earlier findings in rats and cats Finberg et al. Drug interactions Coadministration of SSRIs and

other serotoninergic substances to tranylcypromine is contraindicated due to the risk of serotonin syndrome. With moclobemide great caution should be exercised with this combination. Severe, sometimes fatal, interactions between nonselective, irreversible MAOIs, moclobemide as well as selegiline and pethidine and dextromethorphan have been reported. Indirectly acting sympathomimetics tyramine, ephedrine, pseudoephedrine should be administered with caution in patients treated with MAOIs Dingemanse, The elimination of moclobemide is significantly reduced by cimetidine making dose adjustment necessary. Although selegiline has been reported to have antidepressant actions when combined with 5-hydroxytryptophan Mendlewicz and Youdim, MAO-B-inhibitors may not be safe enough to avoid the "serotonin-syndrome" when given in adjunct to serotonin-reuptake inhibitors SSRIs to treat depression and anxiety in PD patients. However, a clinical trial with a biostatistic power relevant to give a definite answer to the problem is missing. Therefore MAO-B inhibitors have not to be combined with drugs stimulating the serotoninergic system. Meperidin plus selegiline has been reported to be dangerous as it causes severe hypertension Zornberg et al. Selegiline transdermal without tyramine restriction revealed no acute hypertensive reactions in trials, until more data are available, foods that are rich sources of tyramine should be avoided, however. As described by Chen and Swope CYP1A2 inhibitors cimetidine, fluvoxamine, ciprofloxacin increase the area under curve of rasagiline, while CYP1A2 inducers like omeprazol decrease it, as it may decrease in heavy smokers. Minor time-dependent mechanism-based inhibition of CYP2D6 has been described for selegiline and moclobemid in experimental designs; the significance in human beings remains to be investigated Polasek et al. Expert commentary While selective MAO-B-inhibitors demonstrate a significant benefit in PD and improve motoricity and motor fluctuations eventually causing disease-modification in general MAOIs to date play a subordinate therapeutic role in the treatment of depression in PD compared to SSRIs or reboxetine, a selective noradrenergic reuptake inhibitor. This attitude is primarily due to the risk of adverse effects and compliance problems e. Moclobemide according to its favourable adverse effect, interaction and toxicity profile can be used in depressed Parkinson patients when activating properties are necessary, especially. Overall, the clinical use of MAOIs may be limited by the possible adverse effects of restlessness and insomnia - but see rasagiline. As far as long term and prophylactic treatments are concerned, the place of MAOIs still has to be verified as antidepressant or antidementive drugs in PD Tariot et al. Controlled studies are urgent needed for final evaluation and recommendations. Five-year view It would be worthwile to perform clinical studies to demonstrate the capacity of MAO-B inhibitors as antidepressants and antidementive drugs. The pharmacological properties of aminoindan have to be elucidated as they may be neuroprotective Bar-Am et al. Key issues Head-to-head clinical trials are necessary to demonstrate disease-modification using improved delayed-start-study designs with selegiline and rasagiline. Aminoindan has to be tested in vivo in order to get insight into its anti-parkinsonian efficacy. The many molecular biological and -genetic data evolved from in-vitro studies have to be confirmed in in-vivo experiments to prove relevance in human beings. In addition, the respective role of MAO-A has to be elucidated in more detail.

Chapter 2 : Stories by Peter Riederer - Scientific American

Monoamine oxidase (MAO), discovered in the s by Balschko, is one of the most important enzymes in neurotransmitter metabolism. MAO inhibitors have played a major role in our understanding of the functional roles of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) neurotransmission in the CNS.

Is Victory in Sight? L-dopa, the mainstay of current drug therapy was introduced in and since then hundreds of research papers have been published on the disease. It is more common among men than among women and also seems to be more widespread in northern countries. The incidence of the disease increases with age although aging itself is not believed to be a causative factor. At this time there is no medical cure for the condition, but drugs that alleviate the symptoms and slow the progress of the disease are available The tremor is most evident at rest and disappears with movement. Environmental and Dietary Factors Parkinson-like symptoms can also occur as a result of head injuries, carbon monoxide poisoning or poisoning by pharmaceutical or other drugs. The loss of dopamine production affects the balance between dopamine and acetylcholine in the brain with the result that messages to the muscles become garbled. The idea that oxidative stress, i. It is believed that iron helps catalyze the free radical reactions that destroy the dopamine-producing cells 2,8, Recent research has linked high aluminum levels in drinking water to acid rain that leaches the aluminum out of the soil and transfers it to the ground water 4,28, The same study also showed that diets high in vitamin C and beta-carotene provide significant protection Unfortunately, high levels of uric acid may cause heart disease and gout, and as a matter of fact, the overall mortality rate in the high uric acid group was about 30 per cent higher than in the low uric acid group. Stanley Fahn of Columbia University. Thus it is likely that it was vitamin C by itself or its combination with vitamin E that was the active component in Dr. This fits with a later finding that vitamin E, a fat-soluble vitamin, does not readily cross the blood-brain barrier nor does it accumulate in the cerebrospinal fluid that bathes the brain 5, Vitamin C, on the other hand, while not crossing the blood-brain barrier does enter the cerebrospinal fluid and can be found there in concentrations proportional to dietary intake Clinical trials are, however, still required to support this hypothesis Conventional Treatment Meanwhile, what can be done for people who already have the disease? Conventional medical treatment relies heavily on l-dopa levo-dihydroxy-phenylalanine a dopamine-precursor that can cross the blood- brain barrier and is converted to dopamine in the brain. L-dopa is now rarely used by itself, but rather in combination with carbidopa Sinemet or benserazide Madopar that protects it from breaking down before it reaches the brain tissue. As l-dopa must compete with other amino acids in crossing both from the gut to the blood stream and from the blood stream to the brain it is usually recommended that it be taken between meals rather than with meals 1,2,8, After four or five years of increasing dosages their effect becomes sporadic and unpredictable the "on-off syndrome" and patients become increasingly helpless and depressed. There is also evidence that the use of l-dopa medications may lead to a deficiency of B vitamins, especially niacin and vitamin B It works by blocking the breakdown of dopamine in the brain. Anticholinergenic drugs work by reducing the amount of acetylcholine produced in the brain and thereby redresses the imbalance between dopamine and acetylcholine. They are no longer recommended for older patients as they have serious neuropsychiatric side-effects 7,8. This is now changing. Supplementation with vitamin C and E markedly slows the progression of the disease in its early stages. Other antioxidants such as coenzyme Q10 and proanthocyanidins may be equally or more effective - however, this remains to be proven in clinical trials. Supplementation with vitamin B complex may also be necessary, especially for patients who take l-dopa medications. The timing of protein intake can markedly increase the effectiveness of l-dopa and thereby lead to reduced dosage requirements. Researchers now recommend that protein intake be kept as low as possible and that protein be included primarily in the evening meal 47, Australian researchers have found that broad beans Vicia faba is an extremely good source of l- dopa and can, in some cases, actually replace l-dopa. A g serving of broad beans including the pods provides about mg of l-dopa and in addition, a significant amount of

proanthocyanidins. The broad beans remain effective even if canned or frozen, but should always be consumed whole as the pod has been found to have the highest concentration of l-dopa. Medication dosage may have to be adjusted if broad beans are consumed on a regular basis 49, At present the best preventive strategy is to limit the intake of animal fats and sugar, eat a diet rich in fruits and vegetables, avoid toxic metals and an excessive iron intake, and insure an adequate intake of antioxidants. These preventive measures may also be useful in slowing down the progression of the disease. Internal Medicine, 3rd edition, Little, Brown and Co. Scientific American, January , pp. Journal of the American Geriatrics Society, Vol. Postgraduate Medicine Journal, Vol. American Journal of Medicine, Vol. British Medical Journal, Vol. International Journal of Epidemiology, Vol. Dietary carcinogens and anticarcinogens. Free radicals, antioxidants, and human disease: Oxidative damage in neurodegenerative disease. Degeneration of nigrostriatal dopaminergic neurons increases iron within the substantia nigra: Iron induces degeneration of nigrostriatal neurons. Brain Research Bulletin, Vol. Alterations in levels of iron, ferritin, and other trace metals in neurodegenerative diseases affecting the basal ganglia. Annals of Neurology, Vol. Transition metals, ferritin, glutathione, and ascorbic acid in Parkinsonian brains. Journal of Neurochemistry, Vol. Cadmium-induced alterations in blood-brain barrier permeability and its possible correlation with decreased microvessel antioxidant potential in rat. Human and Experimental Toxicology, Vol. The Lancet, August 1, , pp. Advances in Dental Research, Vol. Neurocognitive effects of aluminum. Archives of Neurology, Vol. High aluminum concentrations in well water of southern Lower Saxony sandy soil areas caused by acid precipitation: Rinsho Shinkeigaku Clinical Neurology , Vol. American Journal of Epidemiology, Vol. American Journal of Clinical Nutrition, Vol. New England Journal of Medicine, Vol. Deoxynucleoside and vitamin transport into central nervous system. The normal and pathological physiology of brain water. Advances and Technical Standards in Neurosurgery, Vol. The biology of ascorbic acid. Antiparkinsonian therapies and brain mitochondrial complex I activity. Niacin depletion in Parkinsonian patients treated with L-dopa, benserazide and carbidopa. Condensed proanthocyanidins of fababeans. Journal of the Science of Food and Agriculture, Vol. Behavioral relaxation training for tremor disorders in older adults. Biofeedback and Self Regulation, Vol.

Chapter 3 : ParkinsonÂ's disease

*Supplementa) [Peter Riederer, Heinz Reichmann, Moussa B. H. Youdim, Manfred Gerlach] on calendrierdelascience.com *FREE* shipping on qualifying offers. This book gives a comprehensive overview on current clinical and basic research issues related to Parkinson's disease and its related disorders.*

To investigate these hypotheses, many researchers have applied molecular biology techniques to the study of neuronal cell death in these conditions. In this article, we discuss recent findings of gene expression in PD that may elucidate the usage of specific new biomarkers for sporadic PD and point to novel drug developments. Proteins are critical for a wide range of intra- and ray technology. These methods allow the characterization of extracellular activities, including enzymatic, regulatory and several profiles of global gene expression, as well as screening structural functions. In the past transcriptome, the collection of all mRNAs in a cell, is ex- five years, transcriptomics and proteomics have become the pressed in the brain. Changes in mRNA expression can result most preferred methods for large-scale gene expression assess- in phenotypical and morphological modifications. Although these methods in patterns of expression of multiple genes can offer new are more elaborate compared with microarrays, they provide data concerning the existence of regulatory mechanisms and the possibility of revealing novel unknown genes. The study biochemical pathways. Therefore, the study of mRNA expres- of global gene expression allows us to gain an understanding sion patterns in neurodegenerative disease may reveal the of the mechanisms of neuronal cell death in many diseases involvement of mechanisms of oxidative stress. Riederer P et al. These authors were able to generate ronal cell culture [2]. In this review, we discuss recent findings specific RNA fingerprints with high resolution from pheno- on gene expression of the substantia nigra pars compacta type-specific single neurons. Using DD, the same research SNpc from post-mortem sporadic PD patients affected by group compared mesencephalic dopaminergic neurons con- degeneration of dopamine neurons. Their analysis demonstrated that 64 expressed 2. One of the genes found to be upregulated The study of post-mortem tissues is made difficult [3,4] by in the Lewy body-containing neurons is the ubiquitin specific the scarce availability of brain tissues. Thus, only very peptidase 8 USP8. As in the previous study, this observation recently have several research groups managed to study gene points to the involvement of protein misfolding and degrada- expression in human PD patients. However, comparison of tion in PD. The stress 70 protein chaperone, microsome- results produced by different groups is made difficult by vari- associated, 60 kDa STCH showed downregulation in the ations in the preparation of the substantia nigra SN tissue. In a further neuromelanin-containing dopamine neurons are located. The human post-mortem study of controls [9], a comparison was first study on gene expression profiles was carried out on the made between the nigrosome within the SNpc prone to degen- SN and adjacent midbrain tissues of two normal patients using erate in PD and the central grey substance, which is resistant to SAGE and revealed SN genes within five large genomic the disease. Immunolaser-microdissection-captured neurons linkage regions [5]. Genes such as transcription elongation were identified by anti-tyrosine hydroxylase quick immunos- factor A SII -like 1, apolipoprotein J, ferritin heavy polypep- taining and melanization. RNA fingerprinting was performed tide 1 and betamicroglobulin were amongst the 20 most according to Lu et al. Our research group was able to show, for the first whereas SNpc dopaminergic neurons expressed the gene time, specific gene expression patterns in post-mortem SNpc APLP2, known to be of importance in cell-death mechanisms. This study identified decreased expression of 68 genes in gene composition and gene expression, which are important and enhanced expression of 69 other genes in the SNpc of to improve understanding of cell-death sensible regions and PD patients compared with controls. Classification into give limits for neuroprotective strategies based on both genetic functional groups revealed that genes related to signal trans- targets and pharmacological manipulation of gene expression duction, protein degradation e. Such data clearly demonstrate two impor- functional impairment of an entire repertoire of proteins, tant points: These ations in three different brain regions of PD patients the SN, pu- results have

shed light on the molecular mechanisms impli- tamen and area 9 using Affymetrix GeneChip arrays. A striking cated in PD and may explain how misfolded proteins and ubiq- similarity to our results was found in all three brain regions. The analysis of gene expression in homogenates of human Hauser et al. For such studies, more sophisticated methodologies palsy and fronto-temporal dementia with parkinsonism using are required. Single-cell analysis, using laser capture Affymetrix GeneChip arrays. They found genes Please cite this article in press as: Schematic diagram of major gene and neurochemical alterations in human SNpc of PD. Gene expression analysis of SNpc of PD has confirmed and extended the previously established complexities by which dopaminergic neurons degenerate. Free labile iron itself can cause OS, aggregation of a-synuclein and degradation of iron regulatory protein 2 IRP2 via activation of egl nine homologue 1 Caenorhabditis elegans EGLN1 , which is a key iron and OS sensor. Aldehyde derivatives of dopamine metabolism are highly neurotoxic and aldehyde dehydrogenase ALDH is the key enzyme for their me- tabolism to inert acidic metabolites homovanillic acid and dihydroxyphenylacetic acid. Significant evidence has been provided for involvement of protein misfolding in dopamine neuronal death. This protein processing is exacerbated if some of the 26S proteasome subunits PSM are downregulated, as observed in several studies, since they are an integral part of the regulatory and catalytic activity of the proteasome. In addition, the ubiquitin activating enzyme-1 UBE1 seems to alter its expression, which may influence the SCF process. The decreased expression of the chaperone HSC may affect the correct folding of several proteins that are specifically ubiquitinated by the co-chaperone carboxyl terminus of HSC interacting protein CHIP , as well as parkin-CHIP-mediated ubiquitination, and may increase aggregation of a-synuclein and iron-induced OS. Another protein involved in this processes was found to have a decreased ex- pression in PD: Red boxes are for upregulated genes, and blue boxes are for downregulated genes. Sharp arrows indicate positive inputs, and blunt arrows are for inhibitory inputs. Tables 1 and 2 show the factors that palsy and fronto-temporal dementia with parkinsonism and con- may be responsible for such discrepancies. There were 12 genes common to all disorders. Again, as in of gene expression profiling is a discovery-based procedure all other three studies, four pathways were shown to be altered in and therefore it is highly suitable for the study of idiopathic PD SN substantia nigra: However, when several strategies ficking and nuclear-encoded mitochondrial genes. These new findings may help to develop new hypotheses con- Table 1 cerning the aetiology of the disease and may provide a better di- Confounding clinical factors influencing gene expression profiling agnostic tool for clinicians. We have assembled these findings Pathological stress into a cascade of events which may show the relationship between Pre-mortem clinical evaluation oxidative stress and these gene alterations and cell death Fig. Agonal state The reasons for the existence of discrepancies between a Chronic medication various gene expression studies performed with human post- Time course of disease Variation in patient polymorphism profiling mortem brain tissue and b those data obtained from studies Please cite this article in press as: The benefits of microarrays as a tool for studying neuropsy- Small numbers of cells representative of population of cells of interest? Drugs Today ;40 2: Microarray data analysis Trends Pharmacol Sci ; Whole tissue vs single-cell gene arrays in the same biological samples Effect of agonal and postmortem factors on gene expression profile: Multiregional approach to be used Biol Psychiatry ; Biochemical and molecular studies using human autopsy brain tissue. Hum Mol Genet ; Furthermore, Rechavi G, et al. Gene expression profiling of parkinsonian substantia BNEII-based studies will be able to answer the question of nigra pars compacta; alterations in ubiquitineproteasome, heat shock how clinical factors influence gene expression analysis. J Neural Transm ; Gene expression profiles derived from single cells in human postmortem brain. Brain Res Brain Res Protoc ; Cell type- well as proteomic profiling. One inherent problem with gene specific gene expression of midbrain dopaminergic neurons reveals mol- expression studies is that not all changes in gene expression ecules involved in their vulnerability and protection. Hum Mol Genet can always be correlated with specific proteins. Expression profiling of substantia nigra in Parkinson disease, progressive Acknowledgements supranuclear palsy, and frontotemporal dementia with parkinsonism. J Neurosci Res ;85 Please cite this article in press as:

Chapter 4 : MAO-inhibitors in Parkinson's Disease

Parkinson's Disease- Part I (7/17/11)- A new study shows that, in spite of the fact that the FDA requires a "black box" warning label on all anti-psychotic drugs for Parkinson disease patients who are suffering from dementia, the usage of the drugs continues to thrive.

The results of the study were published in a recent edition of the Archives of Neurology. The researchers examined medical-record data from the Department of Veterans Affairs in fiscal years and Daniel Weintraub, a psychiatry and neurology professor at the Perlman School of Medicine at the University of Pennsylvania was the first author or the study. It is the first transdermal system for the treatment of the disease that has been approved by the agency. At the end of six months, patients who received Execelon did "significantly better" on a scale that measures mental processes than patients who received a placebo. The patients who received the Exelon had significant adverse gastrointestinal reactions. Other significant adverse reactions included vomiting, anorexia, stomach pain and loss of strength. Some patients experienced a worsening of their tremors. Other studies have indicated that safinamide in mice slows the progression of the disease. Trials for patients in the U. The results thus dealt a blow to the hope that infusions of brain tissue from aborted fetuses could reverse the degenerative brain condition. An earlier study, led by Curt Freed of the University of Colorado came up with similar findings. In both studies researchers were not able to find any measurable improvement in tests of motor and other skills. In fact both studies found severe side effects such as uncontrolled motions of the limbs. The researchers had hoped that the new cells capable of making dopamine could treat the symptoms, and prevent the disease from worsening. The researchers have revised their clinical models and safety protocol several times, and have conducted five sets of tests in rats and a safety-test in seven primates. In a paper published in the journal Science, the researchers stated that the genes, inserted into viruses and injected into rats, appeared to slow the progression of the disease. The gene therapy involves injecting the virus that will deliver the gene into nerve cells in the affected area of the brain. It is believed that these affected nerve cells became overactive due to a lack of dopamine. The researchers are now awaiting final approval from a hospital review board before beginning the small clinical trial, which was approved by the FDA on August 2nd. The prospective patients are all younger than 65, have had the disease for over 5 years and are being selected through North Shore-Long Island Jewish Health System in New York. David Edelberg, head of neuroscience at North Shore is working with the researchers. In the Pharmacia study, similar comparisons were made during four years of testing on a group of 82 patients. Mirapex, has been on the market for about 5 years, and was co-developed with Boehringer-Ingelheim GmbH of Germany. Neurodegeneration in PD is associated with a cascade of events that may also involve mitochondrial abnormalities, excitatory amino acids, a rise in intracytoplasmic free calcium, cytokines and trophic factors. In general, PD is a disorder that manifests clinically with a variety of movement impairments. James Parkinson first defined it in He described PD as the "saddest of all diseases". Each year about 50, individuals are diagnosed with this neurodegenerative disease. It is more common among men than among women and also seems to be more widespread in northern countries. The incidence of the disease increases with age although aging itself is not believed to be a causative factor. This treatment replenished brain dopamine levels in the basal ganglia putamen and caudate. Levodopa treatment is associated with development of motor complications such as the "wearing off" of beneficial therapeutic effect and dyskinesia. L-dopa is the mainstay medication used to treat PD. It is a palliative treatment, with research still going on to develop an understanding of the etiology the pathogenic biochemical pathways that lead to clinical symptoms of the disease. Genetic dissection of neurodegenerative disease. Clinical Neuroscience Research Journal ; 1: This is an excellent clinical neuroscience review of the major neurodegenerative diseases. Higher doses are required with the passage of time to effectively manage the treatment. A new treatment has been proposed by Avigen, Inc. Newer treatment steps are being explored. One treatment, a surgical procedure, involves transplanting

fetal nerve tissue into the brains of PD patients to replace dopamine neurons that have been lost. The goal is to replace lost dopaminergic neurons or disrupt aberrant basal ganglia circuitry. This method is usually used in late-stages of the disease. The literature indicates that this method is not always successful. A newer method being explored involves a strategy to halt the continuing loss of dopamine neurons through a potent stimulator of dopamine neuron growth. This involves a substance known as glial cell line-derived neurotrophic factor GDNF. A recent research article in Science ; The researchers conclude "[T]hese data indicate that GDNF delivery using a lentiviral vector system can prevent nigrostriatal degeneration and induce regeneration in primate models of PD and might be a viable therapeutic strategy for PD patients. As geneticists explore the nature of this disease, they realize it is a multifactorial disease, with the rare early onset form of the disease being an inherited autosomal dominant disease. There is some evidence that the mutation in the human alpha-synuclein gene is associated with development of PD and that this single gene deficit may well be sufficient to account for the PD phenotype. How this gene leads to PD is unknown. Alpha -synuclein is a presynaptic protein that is thought to be involved in neuronal plasticity. There are probably also genetic components to the common late-onset forms of PD, but until we have a fuller understanding of the causes of this disease, L-dopa will remain the first line therapy. Medical treatment should be started when functional disability appears, which is a different threshold for each patient. For patients below 65 years old, or above 65 years old but with preserved mental function and with no severe comorbidity, initial monotherapy with a dopamine agonist is advisable. This approach appears to delay the appearance and reduce the amount of late motor complications with subsequent levodopa treatment. Levodopa in combination with carbidopa is the most effective medication for treatment of motor symptoms of PD. Exacerbation of postural and action tremor can occur with levodopa. Tolcapane Tasmar has already caused serious hepatotoxicity and was withdrawn from the market in Canada, but is still available in US. Adverse effects of entacapone: Diarrhea, and orange discolorations of urine. No hepatotoxicity has been reported. Common symptoms of PD include: The above symptoms do not develop all at once, nor do they manifest themselves in all cases of the disease. They are dependent on the progressive stage of the disease. Common adverse effects of all L-dopa medications include: Drug and Aging ; 16 1: The most frequent challenge in diagnosing Parkinson Disease is the conditions of essential tremor and multiple systems atrophy. Parkinson disease has three stages of development: Some of the references used for this article: Journal of the American Geriatrics Society, ; 45 2: Scientific American, January , pp.

Chapter 5 : Moussa B.H. Youdim | Revolvy

Understanding Parkinson's Disease Scientific American January 59 The Authors MOUSSA B. H. YOUDIM and PETER RIEDERER have collaborated since Youdim, a.

Chapter 6 : Peter Riederer - Wikipedia

Understanding Parkinson's Disease. The smoking gun is still missing, but growing evidence suggests highly reactive substances called free radicals are central players in this common neurological.

Chapter 7 : Genomic aspects of sporadic Parkinson's disease | Edna GrÃ¼nblatt - calendrierdelascience.c

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Chapter 8 : Parkinson's Disease and Related Disorders : Moussa B. H. Youdim :

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*Moussa B H Youdim 1, * and Y S Bakhle 2 * Selective inhibitors of MAO-B have found a therapeutic role in the treatment of Parkinson's disease and further.*

Chapter 9 : Moussa B.H. Youdim - Wikipedia

Moussa B. H. Youdim. Peter Riederer Redox imbalance Received: 26 July / Accepted: 30 July / Published online: 10 September Parkinson's disease.