volume 30 | number 2 | pages 101–166 | April 2010

Autonomic & Autacoid Pharmacology

WILEY-BLACKWELL

ISSN 1474 8665 (Print)
ISSN 1474 8673 (Online)

PLENARY LECTURES

Autonomic & Autacoid Pharmacology
2010, 30, 101–165

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A pharmacotherapy of neurodegenerative diseases

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Neurodegenerative diseases are chronic, slowly progressive diseases that cause loss of specific nerve cells. They are a heterogeneous group of diseases as regards to the specific type of involved nerve cells and the predominating clinical symptoms. The common unifying point is the vulnerability of specific nerve cells, the common pathophysiological mechanisms and therapeutic strategies.

The neurodegenerative diseases are classified pathomorphologically according to the dominating protein deposited in the cells. Synucleinopathies are a group of neurodegenerative proteinopathies with common pathological lesions, expressed as aggregation of modified alpha-synuclein protein in some populations of neurons and glia. The abnormal filamentous aggregations of modified alpha-synuclein protein are the main component of Lewy bodies, dystrophic neuritis (of Lewy), and filaments of Papp-Lantos in the oligodendroglia and neurons of patients with multiple system atrophy. They are associated with degeneration of the involved brain regions. Synucleinopathies include the Lewy body disease, dementia with Lewy bodies, Parkinson's disease, multiple system atrophy, Hallervorden-Spatz' disease, the motoneurone disease and the group of taupathies. Most common and most successfully treated is the Parkinson's disease.

The nowadays treatment of Parkinson's disease is symptomatic, neuroprotective and restorative. The aim of the symptomatic treatment is to restore the dopamine deficit, to improve the everyday activities and the quality of life. The neuroprotective treatment has effect on the pathophysiological mechanisms of the disease and is able to delay the progress of the disease. The restorative treatment uses different surgical methods to improve the functions.

The symptomatic treatment is connected with drugs that increase the synthesis of brain dopamine, stimulate postsynaptic dopamine receptors in the striatum, inhibit the reuptake of dopamine in the pre-synaptic structures and inhibit some enzymes connected with the dopamine metabolism. There are some data that Levodopa may accelerate the progression of the disease. The increased dopamine turnover causes oxidative stress generating free radicals and thus accelerates the progression of the disease. Patients enter in the phase of complicated Parkinson's disease 5 years after the onset of Levodopa therapy. That's why the modern treatment demands applying of Levodopa spare therapy. This means that treatment should be started with non Levodopa drugs that influence parkinsonian symptoms and after that they have no more effect. Low-doses Levodopa is added to the treatment. Some of these drugs (Rasagiline, Selegiline, Amantadine and Dopamine agonists) are supposed to have some neuroprotective effects and to delay the progression of the disease.

Starting treatment with neuroprotective drugs from the onset of the disease, when the symptoms are mild is supposed to delay the progression of the disease and patient's disability and to postpone the onset of Levodopa treatment. However there are still no proved data that any of the drugs have neuroprotective effect.

The main parkinsonian symptoms – rigidity and bradykinesia are well influence by the dopaminergic treatment, while the effect on tremor is poor. Moreover the disturbances of speech, swallowing, postural stability and freezing phenomena are also not well affected by the therapy. The same is true about the neuropsychological, autonomic and sleep disturbances.

The most important point in the decision for the treatment is the presence of cognitive disturbances. If the patient has no cognitive impairment and the parkinsonian symptoms are mild without disability, it is better to start treatment with rasagiline or selegiline in order to delay the progression of the disease. If the patient has cognitive deficit and parkinsonian symptoms, it is better to start treatment directly with Levodopa as other drugs may deteriorate the cognitive impairment. Patients with onset of the disease over 70 years should be treated directly with Levodopa, as the side effects from long term Levodopa treatment are not pronounced in this age.

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The neurologist has often the difficult task how to choose a strategy for the patient – to try to improve the symptoms as well as possible or to think about the future of the patient and to only partially treat his symptoms. It is a difficult decision to start mono- or poly- therapy, to start with the most effective Levodopa drugs or to postpone Levodopa having in mind the long term side effects. Having in mind that Parkinson's disease is a chronic one, and the patient needs treatment for a long period of time, the neurologist should consider the duration of the treatment efficacy and the complications from the treatment. However, in the modern treatment there are a lot of possibilities apart from Levodopa.

One of the disadvantages of standard Levodopa formulations is the short plasma half-life and the consequent fluctuations of the serum concentration. This is the main reason for the movement complications following long term Levodopa treatment. This problem is partially solved with the controlled released Levodopa formulations (Madopar HBS, Sinemet CR).

The COMT (cathechol-ortho-methyl transferase) inhibitors are used combined with Levodopa in order to increase the bioavailability and prolong the clinical efficacy. These drugs block the degradation of Levodopa without increasing the maximal plasma concentrations. Entacapone is a potent and selective inhibitor of COMT already used 10 years in the clinical practice. The drug has effect on the parkinsonian symptoms and gives the possibility for decreasing the amount of Levodopa by 25%.

Rasagiline is a selective, non reversible MAO-B inhibitor of second generation. It may be used once daily, without titration and has no amphetamine metabolites that deteriorate cognitive functions. Thus in contrast to selegiline it causes no hallucination and dyskinesias. There are some data that the drug is neuroprotective by reducing oxidative stress and apoptosis and may delay the progression of the disease.

The glutamate antagonists – Amantadines are antagonists of N-methyl D-aspartate receptors (NMDA) and thus tend to normalize the proportion of dopamine and glutamate, decreasing the level of glutamate. The glutamatergic transmission between the subthalamic nucleus and internal globus pallidus is inhibited, as well as the excessive activity by the indirect extrapyramidal pathway. Amantadine as a glutamate antagonist is a neuroprotector and delays the progression of the disease.

Dopamine agonists have common properties to stimulate directly the dopamine receptors (D_2 and D_3), as the molecular configuration is similar to that of dopamine. These drugs have neuroprotective properties and do not cause movement complications. The drugs are first choice in the combined treatment of movement complications due to the longer half-life and the lower needed doses of Levodopa. Pramipexole is a nonergotamine dopamine agonist, which is very effective for patients with early and late Parkinson's disease. It has a good effect on all parkinsonian symptoms and mainly on the tremor. Rotigotine is the first dopamine agonist applied through a transdermal system. It is a nonergotamine dopamine agonist that activates predominantly the D_2 receptors. The drug has advantages for patients with swallowing difficulties. The plasma drug concentrations are more stable for 24 hours and it is applied only once daily. The plasma concentration of the drug is not dependent from the food and stomach evacuation.

Duodopa is a stable gel suspension of Levodopa/Carbidopa, applied through duodenal tube using computerized pump. This mode of application stabilizes the drug serum levels, there is not a pulsate stimulation of the dopamine receptors and thus the motor fluctuations disappear.

Antagonists of A_{2A} adenosine receptors are new and prospective drugs for symptomatic treatment of Parkinson's disease. They are xanthine derivates, synthesized from the natural methylxanthines as caffeine and theophylline. They have effect on all parkinsonian symptoms including tremor. It is supposed that the antagonists of adenosine receptors have also neuroprotective properties, as they inhibit the glutamatergic transmission and the excitotoxicity. Blocking the activity of adenosine receptors causes increased activity of the dopamine receptors.

Despite of the numerous drugs that have effect on parkinsonian symptoms, modern medicine is still not able to suspend the progression of the disease or to significantly lengthen the neurodegenerative process that slowly but steadily ends with disability and death of the patients.