NEW HORIZONS IN THE PHARMACOLOGICAL TREATMENT OF PARKINSON'S DISEASE

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Many of the motoric features that define Parkinson's disease (PD) result primarily from the loss of dopaminergic neurons of the substantia nigra. L-dopa remains at present the most powerful symptomatic drug for the treatment of this condition. However, motor complications of chronic L-dopa treatment have emerged as a major limitations of this therapy. Slowing or delaying the progression of the disease with neuroprotective therapies may delay the need for L-dopa. In the past few years, novel insight into the pathogenetic mechanisms of neurodegeneration in PD have been provided. Mitochondrial function deficiency, increased oxidative stress, apoptosis, excitotoxicity, and inflammation are part of the processes that ultimately result in neurodegeneration. Drugs that are now under clinical scrutiny as neuroprotectant include molecules that combine one or more of the following properties: (1) monoamine oxidase inhibition (rasagiline, safinamide); (2) mitochondrial enhancement (coenzyme Q10, creatine); (3) antiapoptotic activity; (4) anti-inflammatory activity; (5) protein aggregation inhibition; (6) neurotrophic activitiy.
In advanced Parkinson's disease, the combination of disease progression and L-dopa therapy leads to the development of motor response complications, particularly wearing off, on off, dyskinesias and dystonias. The nonphysiologic pulsatile stimulation of striatal dopamine receptors, produced by the currently available dopaminergic drugs, may trigger a dysregulation of many neurotransmitter systems within the basal ganglia, mainly localized on medium spiny striatal neurons. These include alterations of glutamatergic, serotonergic, adrenergic and adenosine A_{2A} receptors. Novel strategies for pharmacological intervention with nondopaminergic treatments hold the promise of providing effective control or reversal of motor response complications. Of particular interest are NMDA and AMPA antagonists or drugs acting on 5-HT subtype 2A, alpha2-adrenergic, and adenosine A_2 receptors. Future strategies may also target pre- and postsynaptic components that regulate firing pattern of basal ganglia neurons, such as synaptic vesicle proteins, nonsynaptic gap junction communication mechanisms, or signal transduction systems that modulate the phosphorylation state of glutamatergic receptors.