PARKINSON'S DISEASE Mitochondrial dysfunction Dopaminergic neuron ം⁺ ത (Striatum) ATP depletion CO 2 The ub iquitin pathway Dopaminergic (Substantia nigra terminal pars compacta) ADB Pi Indirect pathway E2 (Globus pallidus) Proteasome (Subthalamic 🗻 nucleus) Peptides Ubiquitin proteasome system (UPS) disruption Direct pathway E3 (Substantia nigra pars reficulata) Substrate — — Parkin-substrates accumulation Endoplasmic-reticulum-associated E2 °°° + °°° • Polyubiquitination — 🟲 Protofibrils — 🟲 Lewybody AMP PPi K04528 α-Sp22 (α-synuclein aggregation) Endoplasmic reticulum stress Ubiquitin mediated K04243 proteolysis ATP Disrupts dopamine release? K04557 Elevation of A2A receptor transmission Interacts with Adenosine K04266 α-synuclein Dopaminergic 0 synapse cAMP Drop in the Polyubiquitin chain Ubiquitin monomers dopaminergic input K04145 Tyrosine Synaptic vesicle metabolism Dopamine release . Disrupted synaptic vesicle function Unbalanced activity of the striatal output pathways **⊸**ംത Motor <u>~</u>⊙∷ ● Dopamine impairment Dopamine Cell death 0 Oxidative stress ROS The mitochondrial pathway Mitochondria Environmental toxins ~~-**~**⊘___ → Abnormal MPTP MPP+ phosphorylation Complex I deficiency cAMP Rotenone Mitochondrial dysfunction K04633 K04144 Electron Drop in the dopaminergic input transport chain Increased ROS Oxidative ATP depletion phosphorylation : Fall in mitochondrial membrane potential ~ം + ത Apoptosis ADP Pi **-**♣°©°

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