Targeting PERK signaling with the small molecule GSK2606414 prevents neurodegeneration in a model of Parkinson's disease

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 Parkinson's disease (PD) is the second most common neurodegenerative disorder, leading to the progressive decline of motor control due to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Accumulating evidence suggest that altered proteostasis is a salient feature of PD, highlighting perturbations to the endoplasmic reticulum (ER), the main compartment involved in protein folding and secretion. PERK is a central ER stress sensor that enforces adaptive programs to recover homeostasis through a block of protein translation and the induction of the transcription factor ATF4. In addition, chronic PERK signaling results in apoptosis induction and neuronal dysfunction due to the repression in the translation of synaptic proteins. Here we confirmed the activation of PERK signaling in postmortem brain tissue derived from PD patients and three different rodent models of the disease. Pharmacological targeting of PERK by the oral administration of