Precision Medicine in Parkinson's disease:
Past lessons and conquering new frontiers
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ANALYSIS OF INSULIN RESISTANCE AS A RISK FACTOR FOR PARKINSON'S DISEASE

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Recent evidence indicates shared disease mechanisms between Type 2 Diabetes (T2D) and Parkinson's disease (PD), suggesting that T2D may contribute to the development and progression of PD. Insulin resistance, which is the main hallmark of T2D, has also been shown to play an important role in neurodegeneration by altering neuronal metabolism, functionality and survival.
To understand the importance of insulin signalling in the human midbrain we expose human midbrain organoids from healthy individuals and GBA-N409S mutation-carrying PD patients to either high insulin concentrations, leading to insulin resistance, or to low insulin concentrations to restore normal insulin function. We characterise midbrain organoid transcriptional and metabolic profiles in order to identify the most insulin signalling dependent dysregulated cellular processes. Furthermore, we show that insulin resistance compromises dopaminergic neuron maturity and increases cellular death. Our study suggests that defective insulin signalling contributes to the vulnerability of dopaminergic neurons that may lead to the development of PD and aggravates existing PD phenotypes. These results highlight insulin resistance as an important target in PD prevention and therapy