Axonal arborization and energetic metabolism of nigral dopamine neurons: a window into selective vulnerability in Parkinson's disease
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Although the mechanisms underlying the loss of neurons in Parkinson's disease are not well understood, impaired mitochondrial function and pathological protein aggregation are suspected as playing a major role. Why dopamine neurons and a select small subset of brain nuclei are particularly vulnerable to such ubiquitous cellular dysfunctions is presently one of the key unanswered questions in Parkinson's disease research. This talk will present recent data testing the intriguing hypothesis that the heightened vulnerability of these neurons is a consequence of the particular morphological characteristics of these cells, which are long range projections neurons with a highly elaborate axonal arborization and elevated bioenergetic requirements. We find that vulnerable nigral dopamine neurons differ from less vulnerable dopamine neurons such as those of the ventral tegmental area by having a higher basal rate of mitochondrial oxidative phosphorylation, a higher density of axonal mitochondria, an elevated level of basal oxidative stress and a considerably more complex axonal arborization. We found that reducing axonal arborization by acting on axon guidance pathways reduces in parallel the basal rate of mitochondrial oxidative phosphorylation and the vulnerability of nigral dopamine neurons. Our data argue that the heightened vulnerability of nigral dopamine neurons in Parkinson's disease is directly due to their particular bioenergetic and morphological characteristics.

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