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Age-dependent multisystem parkinsonian features in a novel neuromelanin-producing transgenic mouse model

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Parkinson's disease (PD) is characterized by a preferential degeneration of neurons that accumulate with age the pigment neuromelanin, especially neurons from substantia nigra (SN) and locus coeruleus (LC). We aim to characterize the consequences of age-dependent intracellular neuromelanin accumulation in catecholaminergic neuronal populations to understand the relationship between this process and the vulnerability of these cells in PD, as well as its impact on healthy brain aging. We previously generated a rat model exhibiting progressive unilateral SN production of neuromelanin that showed parkinsonian-like neuropathology and motor deficits1. Here, we generated a new neuromelanin-producing rodent model, based on the tissue-specific constitutive expression of human tyrosinase (hTyr) under the tyrosine hydroxylase (TH) promoter (Tg-TH-hTyr), that mimics the bilateral distribution of pigmentation within the aging human brain (i.e. catecholaminergic groups A1-A142). In parallel to neuromelanin intracellular buildup, Tg-TH-hTyr mice exhibited major PD features, including motor and non-motor behavioral alterations, inclusion body formation and degeneration of specific catecholaminergic neuronal groups. Genome-wide transcriptomic analysis of neuromelanin-laden neurons revealed alterations in PD-related biological pathways that correlate with human PD postmortem studies. Our results show that modelling human neuromelanin accumulation in rodents leads to age-dependent catecholaminergic dysfunction and molecular alterations resulting in motor and non-motor deficits, which is relevant to PD pathology and brain aging.

References:

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2Bogerts B. 1981. A Brainstem Atlas of Catecholaminergic Neurons in Man, Using Melanin as a Natural Marker. J Comp Neurol 197(1):63–80.