Spatiotemporal analysis of dopaminergic ALDH1A1$^{+/-}$ subpopulations in the midbrain of a mouse model of alpha-Synuclein (αSyn) overexpression

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Characteristics of Parkinson's Disease (PD) include progressive and preferential degeneration of dopaminergic neurons (DANs) in the substantia nigra (SN) and intraneuronal α-Synuclein (αSyn) inclusions. DANs can be categorized into distinct subpopulations based on location, physiological function and expression profile. Over 60% of DANs in the SN express Aldehyde Dehydrogenase 1A1 (ALDH1A1), a subpopulation identified as selectively vulnerable in post-mortem PD tissue. Evidence suggests complex molecular mechanisms of vulnerability have yet to be delineated. This study characterizes the distribution and transcriptome of ALDH1A1^{+} and ALDH1A1^{-} DANs in a mouse model of αSyn pathology. Mice received intra-nigral injections of AAV-carrying human-αSyn or GFP. Midbrain tissue was collected 3- and 8-weeks post-injection. Neuroanatomical regions and DAN subtypes were identified using immunofluorescence, and spatial transcriptomics was performed using NanoString's GeoMx Digital Spatial Profiler. Results showed diffuse αSyn pathology and increased Snca expression at both timepoints. At 8 weeks, significant DAN loss occurred selectively in ALDH1A1^{-} populations within the SN, with no loss detected in the ventral tegmental area. Spatial transcriptomics identified a robust transcriptomic signature distinguishing ALDH1A1^{+} and ALDH1A1^{-} DANs in naïve and αSyn-overexpressing conditions. αSyn over-expression induced greater transcriptional dysregulation in ALDH1A1^{-} DANs, including downregulation of synaptic vesicle and metabolic pathways, particularly glycolysis. In contrast, ALDH1A1^{+} DANs showed a stronger up-regulation of cholesterol biosynthesis and lipid metabolism, suggesting metabolic rewiring as a potential compensatory mechanism. We provide a comprehensive spatial and temporal characterisation of murine midbrain ALDH1A1^{+} and ALDH1A1^{-} DANs, revealing cell-type-specific transcriptomic and metabolic responses to αSyn over-expression.

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