

## Late-onset parkinsonism in NF- $\kappa$ B/c-Rel-deficient mice: insights into novel drugable targets

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Nigrostriatal dopamine (DA) neuron degeneration, synaptic dysfunctions and neuroinflammation are among the key pathological features of Parkinson's disease (PD). NF- $\kappa$ B factors are considered cardinal players in the progression of the neurodegenerative process, with dual effect on inflammation and apoptosis. While NF- $\kappa$ B/RelA factor acetylated on the lysine 310 residue is responsible for the commencement of apoptotic gene expression, NF- $\kappa$ B/c-Rel factor promotes transcription of anti-apoptotic genes, MnSOD, Bcl-xL and UCP4.

**Aim:** To investigate possible age-associated neurodegeneration in c-Rel<sup>-/-</sup> mice.

**Methods:** WT and c-Rel<sup>-/-</sup> mice were analyzed at 2, 12 and 18 months of age for their motor behaviour and brain neurochemistry and pathology

**Results:** At 18 months of age, c-Rel<sup>-/-</sup> mice exhibited a significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), as assessed by TH IHC and Nissl staining. SNc degeneration was accompanied by a significant loss of DA terminals and a significant reduction of DA and HVA levels in the striatum. Mice deficient of the c-Rel factor exhibited a marked immunoreactivity for fibrillary  $\alpha$ -synuclein in the SNc, increased level of DMT1 and iron. Aged c-Rel<sup>-/-</sup> brain showed increased microglial reactivity, but no astrocytic reaction. In addition, c-Rel<sup>-/-</sup> mice displayed age-dependent deficits in locomotor activity and various gait-related deficits associated with bradykinesia and muscle rigidity. The motor deficits recovered after treatment with L-DOPA. Latest data show that as observed by functional imaging in premotor PD, at an asymptomatic age c-Rel<sup>-/-</sup> mice display early loss of DAT in the caudatum putamen.

**Conclusions:** c-Rel factor is a regulator of SNc resilience to aging. It discloses a new therapeutic target deserving further investigation in PD patients. c-Rel<sup>-/-</sup> mice represent an innovative animal tool to study pathological progression of PD and also model PD preclinical phase of dopamine deficiency (Baiguera et al., *Brain* 135:2750-65 2012).