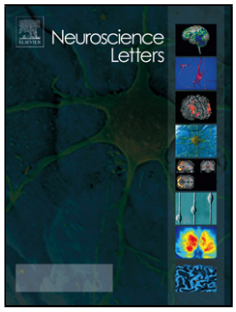

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Suppression of autophagy in the brain of transgenic mice with overexpression of A53T-mutant α-synuclein as an early event at synucleinopathy progression

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Highlights:

Mutant α-synuclein overexpression in mice induces autophagy suppression in the brain

Autophagy decline in young transgenic mice is an early sign of dopaminergic dysfunction

Striatum of transgenic mice is more susceptible to autophagy suppression than s.nigra

Abstract. Transgenic overexpression of α-synuclein is a common model of Parkinson's disease (PD). Accumulation of A53T-mutant α-synuclein induces three autophagy cell response: the inhibition of autophagy caused by the accumulation of α-synuclein, compensatory activation of macroautophagy in response to inhibition of the CMA, and toxic effects of mutant α-synuclein accompanied by the activation of autophagy. The overall effect of long-term overexpression of mutant α-synuclein *in vivo* remained unclear. Here we evaluated the activity of autophagy in the frontal cortex, striatum and s.nigra of transgenic mice with overexpression of A53T-mutant α-synuclein. We revealed low autophagic activity in the dopaminergic structures of 5 m.o. transgenic B6.Cg-Tg(Prnp-SNCA*A53T)23Mkle/J mice as compared to control C57Bl/6J mice. The results were further supported by the data on tyrosine hydroxylase immunostaining that indicated its significant decrease in the striatum but not in s.nigra of transgenic mice and might be related to earlier damage of dopaminergic neurites than somas due to disturbed formation of autophagosomes at neuron periphery. The results evidence possible contribution of suppressed autophagy in the development of PD-like condition as an early event at synucleinopathy progression. Activation of autophagy at early stages of PD seems to be a promising therapeutic