

A DAMAGE TO LOCUS COERULEUS LEADS TO NEUROFILAMENTS LOSS AND INCREASES OF ALPHA-SYNUCLEIN AND P-TAU PROTEINS IN THE PIRIFORM CORTEX

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An early loss of norepinephrine (NE) neurons of the locus coeruleus (LC) takes place in the course of degenerative dementia. This promotes neurodegeneration in target regions primarily within the limbic system. Our recent findings indicate that a damage to LC-NE leads to increased levels of detrimental proteins alpha-synuclein (α-syn) and the phosphorylated tau protein (p-Tau) within the piriform cortex. Here, the effects of a LC-NE neurons depletion were investigated within the piriform cortex to assess the occurrence of neuronal loss or the presence of epigenetic/ultrastructural cellular alterations. C57Bl/6J mice were intraperitoneally treated with saline or the NE neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP4, 60 mg/kg). Seven days after the injection, all mice were killed and dissected brains used for ultra-performance liquid chromatography assessment of NE tissue level and histological analysis of neuronal damage within the piriform cortex by light microscopy and transmission electron microscopy (TEM). Immunohistochemistry and stoichiometric quantification of immunogold particles detected by TEM was carried out to examine the expression level of Smi32 and β-actin, α-syn and p-Tau proteins within the pyramidal neurons of the piriform cortex. RtPCR analysis was carried out to quantify SNCA and MAPT primary transcripts and methylated DNA immunoprecipitation analysis was used to examine SNCA gene promoter methylation. DSP4 treatment led to a significant LC-NE neurons loss with a dramatic NE depletion and neuronal loss within the piriform cortex where the following ultrastructural changes were detected within spared pyramidal cells: (i) destructured/empty cytosol; (ii) loss of neurofilament proteins Smi32 and β-actin; (iii) reduced SNCA promoter methylation with increased SNCA primary transcript and α-syn protein; (iv) increased MAPT primary transcript and higher level of p-Tau protein. These findings demonstrate the fundamental role played by the LC-NE innervation for the integrity of pyramidal neurons of the piriform cortex representing a critical anatomical substrate for degenerative processes associated with degenerative dementia.