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MEETING ABSTRACT

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Protective and toxic role of neuromelanin in brain aging and Parkinson’s disease
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Neuromelanins (NMs) are a family of compounds occurring in all regions of human brain. In particular, NMs accumulate in catecholamine neurons of substantia nigra (SN) and locus coeruleus (LC), which preferentially degenerate in Parkinson’s disease (PD). Then the presence of NM in these neurons has been associated to their vulnerability and a number of studies have shown that NM can play either a protective or toxic role in PD depending on cellular context. In aging, the concentrations of NM attain high values like 3–4 mg/g wet tissue in SN and LC; the decrease of NM concentration occurring in PD can be observed by MRI and this method for imaging neuronal loss is becoming a new tool to confirm PD diagnosis. NM is contained in special autophagolysosomes together with lipid bodies and proteins. The synthesis of NM is controlled by cytosolic concentration of catecholamines which depends on vesicular monoamine transporter 2 (VMAT2) expression. In cytosol, catecholamine adducts with beta-sheet proteins are formed, then these are oxidized to produce protein-melanin that is accumulated in autophagolysosomes, where it is cleaved by proteases and reacts with dolichols to give NM. Synthesis of NM is a protective process because the melanic component is generated through the removal of reactive quinones that would otherwise cause neurotoxicity. Neurons with high NM content have high cytosolic catecholamine content, high vulnerability and low levels of VMAT2; the vice versa is also found. NM can be protective also through its ability to chelate toxic metals and from stable non toxic complexes. Metals accumulated by NM include highly toxic ones like Pb and Hg, in addition to Fe, Zn, Al, Cr and Mo. However, NM can also play a toxic role in PD. Extracellular NM released by degenerating neurons of SN can activate microglia with production of H₂O₂, NO and pro-inflammatory factors then inducing further neurodegeneration, with release of NM, microglia activation and so on. This generates a vicious cycle of neuroinflammation/neurodegeneration which contributes to progression of PD. The major histocompatibility class I complex (MHC-I) is highly concentrated in NM-containing organelles of the SN and LC neurons which degenerate in PD. MHC-I can bind antigens derived from foreign proteins, presenting them on the neuronal membrane. Then CD8+ cytotoxic T cells, observed in proximity of MHC-I-presenting neurons of SN and LC in PD subjects, can target these neurons inducing neuronal death.

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