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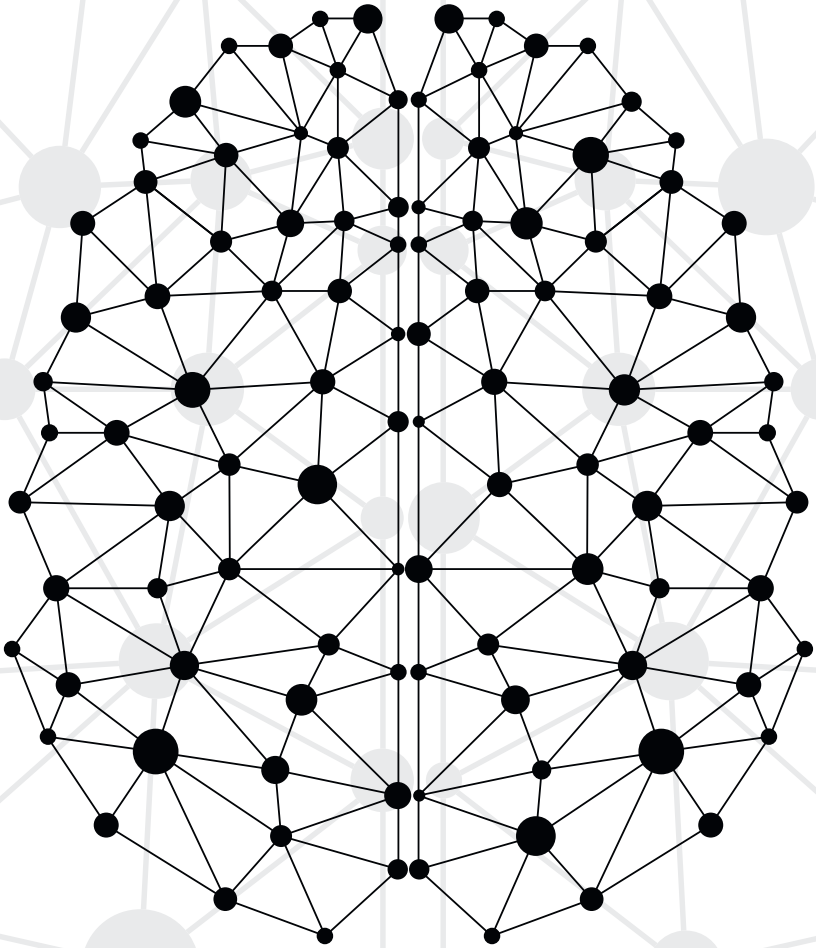

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NOVEL INSIGHT ON THE FINE MECHANISMS OF THE ACTION OF METHAMPHETAMINE WITHIN CATECHOLAMINERGIC NEURONS

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Methamphetamine (METH) is abused worldwide and it represents a threaten for public health. METH exposure induces a variety of detrimental effects. In fact, METH produces a number of oxidative species, which lead to lipid peroxidation, protein misfolding and nuclear damage. Cell clearing pathways such as proteasome (UP) and autophagy (ATG) are involved in METH-induced oxidative damage. Although these pathways were traditionally considered to operate as separate metabolic systems, recent studies demonstrate their interconnection at functional and biochemical level. Very recently, the convergence between UP and ATG was evidenced within a single organelle named autophagoproteasome (APP), which is suppressed by mTOR activation. In the present research study, the occurrence of APP during METH toxicity was analyzed. In fact, co-immune-precipitation indicates a binding between LC3 and P20S particles, which also recruit p62 and alpha-synuclein. The amount of METH-induced toxicity correlates with APPs levels. Specific markers for ATG and UP, such as LC3 and P20S in the cytosol, and within METH-induced vacuoles, were measured at different doses and time intervals following METH administered either alone, or combined with mTOR modulators. Different approaches were used to document the effects of mTOR modulation on METH toxicity and the merging of UP with ATG markers within APPs. METH-induced cell death is prevented by mTOR inhibition while it is worsened by mTOR activation, which correlates with the amount of autophagoproteasomes. The present data, which apply to METH toxicity, are also relevant to provide a novel insight into cell clearing pathways to counteract several kind of oxidative damage.