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The novel organelle autophagoproteasome is recruited to limit methamphetamine toxicity

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Protein clearing pathways represent a powerful physiological mechanism to control homeostasis within eukaryotic cells, while their dysfunction is a key factor in the molecular mechanisms underlying neuronal degeneration. These clearing pathways remove misfolded proteins and altered organelles. Two main pathways named autophagy pathway and ubiquitin proteasome are considered to be prominent in eukaryotic cells. These pathways are commonly viewed as distinct biochemical cascades occurring within specific cytosolic compartments where pathway-specific enzymatic activity is believed to take place. The classic view considers these clearing pathways as distinct depending on various items: different compartmentalization, different substrates, different enzymatic activities and different roles in cell homeostasis. We just described the morphological convergency of autophagy (ATG) and ubiquitin proteasome (UP) pathway to form a novel organelle named autophagoproteasome [1]. This is shown by confocal microscopy and immune-electron microscopy. Both ATG [2] and UP [3, 4] are recruited robustly during methamphetamine exposure playing a pivotal role in methamphetamine toxicity. Methamphetamine dramatically alters autophagoproteasomes which play a critical role in counteracting methamphetamine toxicity. Despite being segregated within a single organelle ATG and UP components undergo a slight different pharmacological regulation. Both pathways are up-regulated along with autophagoproteasome following methamphetamine administration, but UP prevails for low doses while ATG takes over for higher doses of methamphetamine, which demonstrates a common, dopamine-dependent regulation with slight differences for these clearing pathways within a single organelle. ATG and UP component appear to be molecularly bound within autophagoproteasome depending on specific pharmacological stimulation as shown by western blotting of immunoprecipitates. The structure and function of the autophagoproteasome critically relies on mTOR activity for all its components. The fine tuning of mTOR activity is likely to impact significantly methamphetamine toxicity as well as dopamine-dependent pathological conditions.

References

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Keywords
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