PROCEEDINGS
– OF RESEARCH AND PRACTICE IN ALLIED AND ENVIRONMENTAL HEALTH –

# Cellular Mechanisms of 1,3-Dimethylamylamine (1,3-DMAA)-Induced Toxicity

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**Background:** 1,3-Dimethylamylamine (1,3-DMAA) is a chiral sympathomimetic amine formerly used as a nasal decongestant until its withdrawal in the 1980s due to adverse effects such as headaches, nervousness, psychomotor agitation, and tremors [1]. In 2005, it re-emerged in dietary supplements marketed for weight loss, performance enhancement, and recreational purposes [2]. Despite regulatory bans, 1,3-DMAA continues to be detected in doping controls and dietary supplements, raising toxicological concerns. The cellular mechanisms underlying its neurotoxic potential remain incompletely characterized [3]. **Objective:** This study aimed to investigate the cytotoxic mechanisms induced by 1,3-DMAA in a human neuronal cell model (SH-SY5Y), contributing to a better understanding of its toxicodynamics. **Methods:** SH-SY5Y cells were exposed for 48h to 1,3-DMAA ($1.3\times10^{-4}$ to $1.5\times10^{1}$ mM; n=5); mitochondrial metabolic activity was assessed using the MTT assay and the lysosomal integrity through the neutral red uptake (NR) assay. Based on the MTT results, cells were subsequently exposed to the $EC_{20}$ (4.21 mM), $EC_{40}$ (4.91 mM), and $EC_{60}$ (5.59 mM), and changes in intracellular reactive oxygen species (ROS) production and mitochondrial membrane potential ($\Delta\Psi m$) assessed using fluorometric probes. Autophagic features were evaluated using acridine orange (AO) staining to detect acidic vesicular organelles. **Results:** 1,3-DMAA induced concentration-dependent cytotoxicity, with a greater impact on mitochondrial function than lysosomal integrity, as evidenced by lower $EC_{50}$ values in the MTT assay compared to the NR assay (5.24 mM versus 6.36 mM, respectively). 1,3-DMAA induced a concentration-dependent increase in intracellular ROS levels from $EC_{20}$ (236.67%; $p<0.001$) and $EC_{40}$ (211.87%; $p<0.01$) and peaking at $EC_{60}$ (272.05%; $p<0.0001$). In contrast, $\Delta\Psi m$ remained unchanged at lower concentrations, with a significant increase observed at $EC_{60}$ (317.32%; $p<0.0001$). AO staining showed increased acidic vesicular organelles at higher concentrations. **Conclusions:** The concomitant increase in ROS and hyperpolarization of $\Delta\Psi m$ indicate a pro-oxidant state. The AO assay demonstrated progression to autophagy and/or apoptosis. These findings consolidate and provide a mechanistic basis for future studies.

**Keywords:** 1,3-Dimethylamylamine; cytotoxicity; SH-SY5Y cells.

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