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Toxicity of amphetamine-type drugs in rat cardiomyocyte cells involves oxidative stress and the formation of acidic vesicular organelles

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Abstract

Background: Synthetic cathinones (SCs) are recreational psychoactive substances with pharmacological properties resembling those of classical amphetamines, such as 3,4-methylenedioxymethamphetamine (MDMA; *ecstasy*) [1]. Although the use of SCs has been linked to adverse health outcomes, including myocardial infarction and sudden cardiac deaths [2], the underlying cardiotoxic mechanisms are still unknown. **Objective:** This study evaluates the potential *in vitro* cardiotoxicity mechanisms of two commonly abused SCs, 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxymethcathinone (methylone), and compares them with those obtained for MDMA. **Methods:** The H9c2 cell line was exposed for 24 hours to a wide range of concentrations (0.01-15 mM for MDPV; 0.01-20 mM for MDMA and methylone). The cytotoxic response was measured through the MTT assay and the role of oxidative stress was evaluated through the production of reactive oxygen and nitrogen species (ROS/RNS). The formation of acidic vesicular organelles (AVOs) was also evaluated by fluorescence microscopy in cells exposed to EC_{30} or EC_{60} of each drug. **Results:** All compounds decreased cell viability in a concentration-dependent manner. MDPV and MDMA were the most toxic drugs (EC_{50} 1.76, 1.86 mM, respectively), while methylone was the least cardiotoxic derivative (EC_{50} 3.30 mM; $p<0.0001$ *vs.* EC_{50} MDMA; $p<0.0001$ *vs.* overall fit MDMA). MDMA triggered ROS/RNS production only at 0.8 mM ($p<0.0001$ *vs.* control) and MDPV only at 1.6 and 3 mM ($p<0.01$ *vs.* control). In contrast, methylone demonstrated a significant increase for all concentrations between 0.05 mM ($p<0.0001$ *vs.* control) and 12 mM ($p<0.05$ *vs.* control). All drugs prompted the formation of AVOs in a concentration-dependent manner. **Conclusions:** Our findings are the first to show that SCs cause *in vitro* cardiotoxicity, and that oxidative stress and autophagy may play a role in these events. Further research is needed to explore the underlying molecular mechanisms.

Keywords: methylone; MDPV; MDMA; cardiotoxicity; oxidative stress

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References

1. Valente, M.J.; Guedes de Pinho, P. Khat and synthetic cathinones: a review. *Arch Toxicol* **2014**, 88, 15-45.
2. Radaelli, D.; Manfredi, A. Synthetic cannabinoids and cathinones cardiotoxicity: facts and perspectives. *Curr Neuropharmacol* **2021**, 19, 2038-2048.