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Hidden dangers of synthetic cathinones: unveiling the role of oxidative stress in the cardiotoxicity of methylone and 3,4-DMMC

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Abstract

Background: Synthetic cathinones (SCs) are the second most reported class of new psychoactive substances worldwide, according to the United Nations Office on Drugs and Crime (UNODC), with over 100 analogues identified [1]. These recreational stimulants exhibit pharmacological properties similar to amphetamines [2] and have been associated with serious cardiac events, including myocardial infarction and sudden cardiac death [3]. However, the mechanisms underlying their cardiotoxicity remain unclear. **Objective:** This study investigates the cardiotoxic effects of two commonly abused SCs, namely 3,4-methylenedioxymethcathinone (methylone) and 3,4-dimethylmethcathinone (3,4-DMMC), and examines the role of oxidative stress in their toxicity. **Methods:** Rat H9c2 cardiomyoblasts were exposed to methylone (0.01-4 mM) and 3,4-DMMC (0.0005-0.8 mM) for 24 and 48 hours. Cell viability was evaluated using the MTT assay, while oxidative stress was assessed by measuring reactive oxygen and nitrogen species (ROS/RNS) production at multiple timepoints (0.5 to 24 h) at the EC_{50} concentration. Additionally, the protective effects of antioxidants, including ascorbic acid (AA, 0.1 mM), N-acetylcysteine (NAC, 1 mM), and Trolox (TRX, 0.2 mM), were assessed 24 hours after incubation with EC_{40}. **Results:** Both substances decreased cell viability in a concentration-dependent manner, but this effect was not significantly affected by incubation time. 3,4-DMMC showed greater cytotoxicity than methylone at 24 h (EC_{50}: 0.28 mM vs. 0.98 mM, p=0.0013) and 48 h (EC_{50}: 0.18 mM vs. 1.04 mM, $p < 0.0001$). ROS/RNS levels increased over time, reaching statistical significance at 3 h for 3,4-DMMC ($p < 0.05$) and 4 h for methylone ($p < 0.01$), indicating the involvement of oxidative stress. Among the antioxidants tested, only AA effectively attenuated SC-induced toxicity, while NAC and TRX showed no protective effect. **Conclusions:** Our findings demonstrate that SCs induce significant cardiotoxicity *in vitro*, with 3,4-DMMC being more toxic than methylone. Oxidative stress contributes, at least in part, to the cardiotoxic effects of these substances. Notably, AA offers potential protection against SC-induced damage. These results highlight the need for further research to elucidate the precise mechanisms of SC-induced cardiotoxicity and to explore therapeutic strategies.

Keywords: cathinones; myocardial damage; toxicity mechanisms

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