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Neurotoxicity Evaluation of Four Structurally Similar Synthetic Cathinones in a Cholinergic Neuronal Model: a Comparative Analysis

Catarina da Fonseca [1, 2,*], Rui Malheiro [1, 2], Fernando Remião [1, 2], João Pedro Silva [1, 2] and Renata Silva [1, 2]

[1] Associate Laboratory i4HB – Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal.
[2] UCIBIO, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313, Porto, Portugal.

* Correspondence: up201804901@edu.ff.up.pt

Abstract

Background: Synthetic cathinones are potent central nervous system (CNS) stimulants that induce diverse neurological and psychiatric effects such as delusions, hallucinations, and agitation [1]. This fast-expanding class of new psychoactive substances (NPS) represented the majority of those seized in the European Union in 2021 [2]. Despite the growing recreational use, knowledge on their neurotoxic mechanisms, namely during neuronal differentiation, remains limited. **Objective:** This study aimed to compare the neurotoxicity of four structurally-related synthetic cathinones (3-CMC, 4-CMC, 4-CEC, and Ethcathinone), differing in the presence and position of a chlorine in the aromatic ring and in the length of the N-alkyl group, using a well-characterized neuritogenesis in vitro model. **Methods:** Lysosomal integrity, analyzed by the neutral red uptake assay, and reactive oxygen/nitrogen species (ROS/RNS) production, evaluated with the DCFH-DA probe, were assessed in NG108-15 neuroblastoma x glioma cells differentiated into a cholinergic phenotype [induced by serum-starved medium (1% FBS) supplemented with forskolin (30 μM) and retinoic acid (10 μM)], following a 24 h exposure to the tested drugs (1 nM – 1 mM). Results: All synthetic cathinones tested significantly reduced lysosomal integrity and increased ROS/RNS formation. The cathinones with a chlorine in the position 4 of the aromatic ring exhibited more pronounced effects, causing cell viability loss at concentrations $\geqslant$100 μM, while for the others it was only significant for concentrations $\geqslant$500 μM. Moreover, structures with a longer N-alkyl substituent appeared to show higher cytotoxicity (probably related to their higher lipophilicity), with 4-CEC demonstrating greater lysosomal integrity loss (50%) relatively to control than 4-CMC (80%) at 100 μM. **Conclusions:** Halogen positioning within the aromatic ring, as well as their lipophilicity, influenced the cytotoxicity of synthetic cathinones, being seemingly associated with increased oxidative stress. Future research should encompass mechanistic studies, particularly focusing on specific neurogenesis-related processes, to comprehensively unravel the mechanisms underlying neurotoxicity.

Keywords: new psychoactive substances; central nervous system; NG108-15 cells; cytotoxicity; ROS production

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