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Scientific Letters

II TOXRUN
International Congress 2023
27-28 April, 2023 | Porto, Portugal

Poster 59

Mechanisms behind the neurotoxicity of 2C-I and 25I-NBOMe drugs

E. Gil-Martins [1,2,*], A. Borer [1], F. Cagide [2], D. J. Barbosa [3,4], D. Martins [2], C. Fernandes [2], F. Remião [1], F. Borges [2] and R. Silva [1]

[1] UCIBIO – Applied Molecular Biosciences Unit, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal
[2] CIQUP-IMS, Research Center in Chemistry, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal
[3] TOXRUN – Toxicology Research Unit, University Institute of Health Sciences, CESPU, CRL, Avenida Central de Gandra 1317, 4585-116 Gandra, Portugal
[4] Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal

* Correspondence: evagilmartins@gmail.com

Abstract

Background: New Psychoactive Substances (NPS) pose significant health and legal risks worldwide. At the end of 2021, the European Monitoring Centre for Drugs and Drug Addiction was monitoring 886 NPS, 106 of them phenethylamines [1]. Phenethylamine derivatives include 2,5-dimethoxyphenethylamine-based (2C) and *N*-benzylphenethylamine-based (NBOMe) drugs, widely known for their psychedelic effects. However, their toxicological profile remains poorly characterized [2,3]. **Objective:** To address this gap, 2C-I (2-(4-iodo-2,5-dimethoxyphenyl)ethanamine) and its corresponding NBOMe derivative (2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine) were synthesized and their neurotoxic profile evaluated, elucidating potential mechanistic pathways involved in drug-induced cytotoxicity. **Methods:** 2C-I and 25I-NBOMe were synthesized and structurally characterized by nuclear magnetic resonance and mass spectrometry techniques. Neuronal SH-SY5Y cells differentiated into a dopaminergic phenotype and primary rat cortical neurons, which were exposed to the drugs for 24 hours, were used for the *in vitro* experiments. Drugs' neurotoxicity and the impact of MAO-mediated inhibition on drug-induced cytotoxicity were evaluated using the neutral red uptake assay. The capacity of the drugs to generate free radicals was estimated using the DCFH-DA probe and their impact on the intracellular GSH and ATP levels were assessed using the DTNB-reductase-recycling and the ATP bioluminescence assays, respectively. Changes in the mitochondrial membrane potential were investigated using the JC-1 probe. The chromatographic hydrophobicity index (CHI) of the drugs was also evaluated by Fast-Gradient RP-HPLC. **Results:** Both drugs exhibited a concentration-dependent neurotoxic effect, with 25I-NBOMe being more cytotoxic than its counterpart, which supports the drugs' lipophilicity data. MAO inhibition had no significant impact on drug-induced cytotoxicity. No significant changes in ROS production were observed for both drugs, but a significant decrease in intracellular GSH and ATP levels, and significant mitochondrial membrane depolarization was detected. **Conclusions:** The introduction of a NBOMe substituent significantly increased all the evaluated neurotoxic effects, demonstrating the high potential of these drugs to induce severe adverse reactions.

Keywords: new psychoactive substances; neurotoxicity; 2C-I; 25I-NBOMe

Acknowledgments

This research was funded by the Foundation for Science and Technology (FCT, Portugal), in the scope of the projects UIDP/04378/2020 and UIDB/04378/2020 (UCIBIO), LA/P/0140/2020 (i4HB), UIDB/00081/2020 (CIQUP), LA/P/0056/2020 (IMS) and by FEDER/COMPETE POCI-01-0145-FEDER-02839. Eva Gil-Martins (SFRH/BD/146527/2019), Daniel Martins (PD/BD/135122/2017), Carlos Fernandes (2021.04016.CEECIND) and Fernando Cagide (SFRH/BDP/72923/2010) were supported by FCT fellowships from FCT.

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