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In vitro neuro- and hepatotoxic profile of new psychoactive phenethylamines

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Resumo

Introduction: Phenethylamine derivatives (PEAs) rank third in number of monitored substances by the EU Early Warning System [1]. However, since little or no information regarding their toxicology profile is available, they represent a constant danger to public health. **Objectives:** Thus, the main goal of this study was to evaluate the in vitro neurotoxic and hepatotoxic profile of three PEAs -mescaline, 2C-B and 2C-N - and their corresponding N-benzylphenethylamine (NBOMe) derivatives - mescaline-NBOMe, 25B-NBOMe and 25N-NBOMe - as well as explore the mechanistic pathways involved in their cytotoxicity. **Material and methods:** SH-SY5Y cells (dopaminergic phenotype) and HepG2 cells, representing two main target organs for these drugs – brain and liver, respectively –were used to perform all the in vitro experiments. Accordingly, the derivatives (0-2000 µM) cytotoxicity was assessed 24 h after exposure, by the neutral red uptake assay. Their ability to produce free radicals was also measured, using the DCFH-DA fluorescent probe, and the impact of cytochrome P450 (CYP)-mediated metabolism on the compound's cytotoxicity was assessed by inhibiting different CYP isoforms, 24 h after exposure to the compounds. Furthermore, after exposure of SH-SY5Y cells to the derivatives (0-500 µM for 24 h), the intracellular reduced glutathione (GSH) levels were quantified, by the DTNB-reductase-recycling assay and the energy state was evaluated through the quantification of ATP intracellular levels (ATP bioluminescence assay). **Results:** All the tested PEAs (except mescaline) showed remarkable cytotoxic effects towards SH-SY5Y and HepG2 cells, with the addition of an N-benzyl moiety significantly increasing the observed cytotoxic effects. However, no ROS/RNS production was detected for any of the compounds in the tested conditions. Co-incubation with cytochrome P450 (CYP) inhibitors highlighted a potential role for these enzymes in the metabolism of the tested compounds, especially for CYP3A4 and CYP2D6. In SH-SY5Y cells, a concentration-dependent GSH depletion (for all the PEAs) and ATP decline (for all the PEAs except mescaline) was observed, being more pronounced for the NBOMe derivatives. **Conclusions:** In summary, the addiction of a NBOMe moiety to the parent drug significantly increased its cytotoxic effects, and the inhibition of CYP3A4 and CYP2D6 emphasized CYP-mediated metabolism as a potential detoxification pathway for these drugs.

Keywords: neurotoxicity; hepatotoxicity; new psychoactive substances; phenethylamines.

References:

[1] European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2021: Trends and Developments, Publications Office of the European Union, Luxembourg, 2021.