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Assessment of the CYP450 inhibitory potential of LSD, 5-MeO-DMT and mescaline: an *in vitro* study

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Abstract

Background: LSD, 5-MeO-DMT and mescaline are classic hallucinogens known for their recreational use, whose consumption increased in the last decades. Despite some available data on the toxicokinetics of these drugs, little is known about their CYP450 metabolism [1,2,3]. Nevertheless, this information is of crucial relevance to predict drug-drug interactions and understand toxicological phenomena, in particular interindividual variability. **Objective:** This study evaluated the potential inhibition of LSD, 5-MeO-DMT and mescaline over CYP450 isoenzymes (CYP3A4, CYP2D6, CYP2B6 and CYP2A6). **Methods:** The Vivid® CYP450 screening kits were used following the manufacturer's instructions. Concentration ranges tested for each drug were $6.1x10^{-5}$–1.0 mM, $1.95x10^{-4}$–4.0 mM and $6.1x10^{-5}$–1.0 mM for CYP3A4; $9.54x10^{-8}$–1.0 mM, $9.54x10^{-7}$–4.0 mM and $6.1x10^{-5}$–4.0 m for CYP2D6; $2.56x10^{-5}$–2.0 mM, $2.44x10^{-4}$–6.0 mM and $6.1x10^{-5}$–4.0 mM for CYP2B6; and $1.91x10^{-6}$–1.0 mM, $2.86x10^{-6}$–4.0 mM and $2.29x10^{-5}$–1.0 mM for CYP2A6, for LSD, 5-MeO-DMT and mescaline, respectively. Solvent and positive controls of inhibition, i.e., ketononazole (CYP3A4), quinidine (CYP2D6), miconazole (CYP2B6) and tranylcypromine (CYP2A6) were used. Fluorescence was measured for 60 minutes at excitation and emission wavelengths of 415/20 and 460/20 nm, respectively. The half-maximal inhibitory concentration (IC_{50}) was calculated using GraphPad Prism 9.3.0. Five independent experiments were performed for CYP3A4, four for CYP2D6 and two for CYP2B6 and 2A6. **Results:** IC_{50} values of 80.92 µM, 203.27 µM, 97.59 µM for CYP3A4; 0.61 µM, 3.47 µM, 558.53 µM for CYP2D6; 604.68 µM, 653.55 µM, 323.98 µM for CYP2B6; and 54.44 µM, 124.82 µM, 96.35 µM for CYP2A6, were obtained for LSD, 5-MeO-DMT and mescaline, respectively. **Conclusions:** LSD and 5-MeO-DMT have a strong potential to inhibit CYP2D6, which is highly polymorphic and therefore implicated in great toxicological interindividual variability. CYP3A4 which is involved in the metabolism of many drugs and food is also greatly inhibited by LSD and mescaline.

Keywords: hallucinogens; toxicokinetics; psychoactive substances

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