Psychoactive N,N-dialkyltryptamines modulate serotonin transport by at least two mechanisms

*N. V. Cozzi¹, A. T. Shulgin², P. F. Daley³, A. Gopalakrishnan¹, L. L. Anderson¹, J. T. Feih¹, A. E. Ruoho¹

¹Pharmacol., UW Sch. Med. & Publ. Hlth., Madison, WI
²1483 Shulgin Rd, Lafayette, CA

Abstract

N,N-dimethyltryptamine (DMT) is a potent plant hallucinogen that has also been reported in human brain. When ingested, DMT and related N,N-dialkyltryptamines produce an intense dream-like state with colorful visual imagery, altered perceptions of time and space, changes in body image and sensations, and intense mood changes ranging from euphoria to sadness. The hallucinogenic effects of these tryptamines are mediated through various neurochemical mechanisms including activity at monoamine receptors, modification of monoamine uptake and release, and competition for monoamine oxidase enzymes. To further clarify the pharmacology of hallucinogenic tryptamines, we synthesized DMT, N,N-dipropyltryptamine (DPT), N,N-diisopropyltryptamine (DIPT), and N-methyl-N-isopropyltryptamine (MIPT); structures were confirmed by mass spectrometry. The drugs were tested for their abilities to inhibit [³H]5-HT uptake via the plasma membrane serotonin transporter (SERT) and via the vesicle monoamine transporter (VMAT2). The tryptamines were also tested as inhibitors of [³H]paroxetine ([³H]PXT) binding to the SERT and [³H]dihydrotetrabenazine ([³H]TBZOH) binding to VMAT2. SERT-mediated [³H]5-HT uptake and [³H]PXT binding were assayed in human platelets, while VMAT2-mediated [³H]5-HT uptake and [³H]TBZOH binding were assayed in Sf9 cells infected with a recombinant baculovirus expressing the rat VMAT2. Our results show that DMT, DPT, DIPT, and MIPT inhibit [³H]5-HT transport at SERT and VMAT2 at low micromolar concentrations. The tryptamines also inhibited [³H]PXT binding to SERT at micromolar concentrations. The ratio of the Ki value of [³H]PXT binding inhibition-to-[³H]5-HT uptake inhibition was highest for DMT and this is consistent with substrate properties for DMT at the SERT. On the other hand, the ratio was lowest for DIPT, suggesting that this drug is an uptake inhibitor, not a substrate. At VMAT2, the tryptamines did not appreciably inhibit [³H]TBZOH binding to VMAT2 until millimolar concentrations were reached, resulting in consistently high binding-to-uptake ratios. These high ratios are consistent with substrate properties for the tryptamines at VMAT2. Together, these studies reveal two mechanisms whereby hallucinogenic tryptamines modulate serotonin transport.