

Psycho-pharmacology Research



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Pharmacology of novel psychoactive substances, MDMA, and LSD

Our research focus is on the pharmacology of psychoactive substances *in vitro* and in humans. We characterize novel substances (designer drugs) *in vitro* and also investigate the pharmacokinetics-pharmacodynamics of MDMA, LSD, and amphetamines in humans including psychological tests, pharmacogenetics, and functional brain imaging. This work is linked to studies on the acute clinical problems associated with the recreational drug use. In the laboratory, we mainly characterize the receptor interaction profiles of novel psychoactive substances and their cytotoxic effects.

Novel psychoactive substances

Novel psychoactive substances are newly used designer drugs ("internet drugs", "research chemicals", "legal highs") potentially posing similar health risks to classic illicit substances. In the last years we have seen an unprecedented growth in the number of new psychoactive substances on the illicit drug market. Currently, more than one new substance is identified in Europe every week. Information on the pharmacology and toxicology of these substances is important to reduce risks to the public. Many novel psychoactive substances interact with biogenic amine neurotransmitter transporters. Amphetamines including methamphetamine and MDMA inhibit the dopamine, serotonin and norepinephrine transporter and also release these monoamines through the respective transporter. Substances which predominantly release serotonin, similar to MDMA, can be expected to produce MDMA-like effects with serotonergic toxicity including serotonin syndrome, hyponatremia, hyperthermia, and seizures. In contrast, psychostimulants such as methamphetamine or methylphenidate are mostly enhancing dopaminergic neurotransmission. Dopamine mediates the reinforcing and addictive properties of drugs of abuse. The relative dopaminergic to serotonergic properties *in vitro* (dopamine/serotonin transporter inhibition ratio) of a novel substance can be determined as a useful marker for its potential clinical psychotropic and acute toxic effects (Fig. 1).

Mechanism of action of MDMA (ecstasy)

MDMA (ecstasy) acutely induces happiness, emotional empathy, and prosociality. MDMA is used as recreational substance and also investigated as medication to assist psychotherapy in psychiatric patients. We demonstrated a critical role for transporter-mediated serotonin and norepinephrine release in the effects of MDMA in humans. The dual serotonin and norepinephrine transporter inhibitor duloxetine blocked MDMA-induced serotonin and norepinephrine efflux from transporter loaded cells stably expressing the human serotonin or norepinephrine transporter and prevented the MDMA effects in humans. The findings indicate that the psychotropic effects of MDMA in humans depend on transporter-mediated release of both serotonin and norepinephrine. The response to MDMA is also dependent on interindividual genetically-determined differences in the metabolism of MDMA. For example, subjects who are cytochrome P450 (CYP) 2D6 poor metabolizers show higher plasma concentrations of MDMA and associated faster increases in cardiovascular responses to MDMA compared with subjects who are normal metabolizers (Fig. 2).

Pharmacokinetics of MDMA and LSD and effects on emotion processing

Several clinical studies are investigating the use of MDMA and LSD in substance-assisted psychotherapy to treat post-traumatic stress disorders or anxiety in patients with life-threatening diseases. We therefore studied the pharmacokinetics

of MDMA and LSD and the effects of these substances on the processing of emotions in healthy subjects. LSD produced subjective drug effects that lasted up to 12h (Fig. 3a) and correlated well with the concentrations of LSD in the blood plasma over time (Fig. 3b and c). The half-life of LSD in plasma was 3.5 h. In contrast to LSD, the half-life of MDMA is longer (8h) but the effects of MDMA last only up to 6h despite the continued presence of the substance in the body (Fig. 3d). Thus, there is marked acute tolerance to the effects of MDMA. In a controlled setting, both MDMA and LSD dose-dependently increased feelings of closeness and trust and impaired identification of negative emotions including fear and sadness. These effects of MDMA and LSD on emotion processing may be useful for substance-assisted psychotherapy.

Selected Publications

Simmler LD, Buchy D, Chaboz S, Hoener MC, Liechti ME. (2016) *In vitro* characterization of psychoactive substances at rat, mouse, and human trace amine-associated receptor 1. *J. Pharmacol. Exp. Ther.* 357, 134–144

Rickli A, Lüthi D, Reinisch J, Buchy D, Hoener MC, Liechti ME. (2015) Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). *Neuropharmacology* 99, 546–553

Rickli A, Kopf S, Hoener MC, Liechti ME. (2015) Pharmacological profile of novel psychoactive benzofurans. *Br. J. Pharmacol.* 172, 3412–25

Liechti ME. (2015) Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signalling. *Swiss Med. Weekly.* 145, 214043

Schmid Y,ENZLER F, Gasser P, Grouzmann E, Preller K, Vollenweider FX, Brenneisen R, Müller F, Borgwardt S, Liechti ME. (2015) Acute effects of LSD in healthy subjects. *Biol. Psych.* 78, 544–553

Simmler LD, Buser TA, Donzelli M, Schramm Y, Dieu LH, Huwyler J, Chaboz S, Hoener MC, Liechti ME. (2013) Pharmacological characterization of designer cathinones *in vitro*. *Br. J. Pharmacol.* 168, 458–70

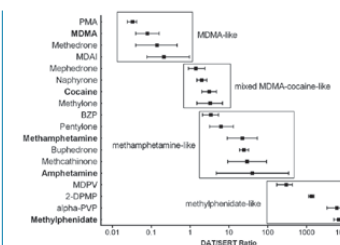


Fig. 1: Relative dopamine/serotonin inhibition potencies of psychoactive substances. Dopamine to serotonin transporter (DAT/SERT) inhibition ratios (mean ± 95% confidence intervals) for novel substances are shown in comparison with those of classic empathogens/entactogens (MDMA, ecstasy) and stimulants (cocaine, amphetamine, and methamphetamine). The ratios derived from *in vitro* studies help to predict the typically unknown clinical toxicity of novel substances. A low DAT/SERT inhibition ratio (<0.1) indicates tenfold greater relative serotonergic vs. dopaminergic activity similar to MDMA. A high DAT/SERT inhibition ratio (>10) indicates greater relative dopaminergic vs. serotonergic activity similar to methamphetamine. A high DAT/SERT inhibition ratio is a pharmacological characteristic associated with more stimulant effects and with higher potential for addiction.

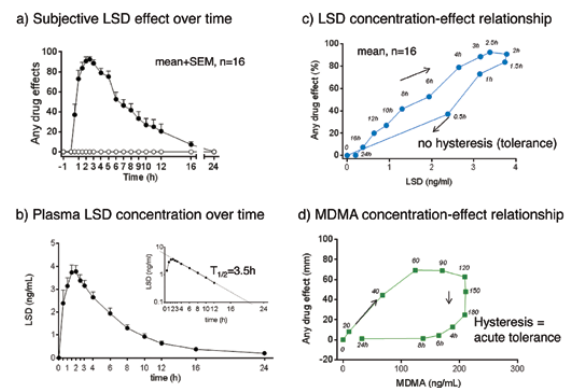


Fig. 3: Pharmacokinetics-Pharmacodynamics of LSD. LSD effects last up to 12h (a) corresponding to its plasma-concentration time curve (b) and exhibiting no hysteresis in the LSD concentration-effect plot (c). In contrast, the MDMA concentration-effect plot shows pronounced hysteresis consistent with acute tolerance (d).

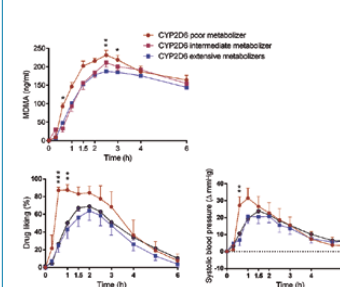


Fig. 2: Pharmacogenetics of MDMA. CYP2D6 phenotypes predicted by genotyping modulate the plasma concentration of MDMA and MDMA-induced increases in blood pressure and subjective drug liking. Effects increased more rapidly in CYP2D6 poor metabolizers (PMs) compared with intermediate (IMs) or extensive metabolizers (EMs). The data are expressed as the mean ± SEM in seven PMs, 19 IMs, and 113 EMs. *P < 0.05, **P < 0.01, ***P < 0.001, PMs compared with IMs or EMs at the corresponding time.