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THE IMPACT OF SELECTED PSYCHOACTIVE SUBSTANCES - COCAINE, AMPHETAMINE, PSILOCYBIN, MDMA, AND KETAMINE - ON THE BODY IN PHYSICAL AND PSYCHOLOGICAL ASPECTS AND THEIR MAIN MECHANISMS OF ACTION: A NARRATIVE REVIEW

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ABSTRACT

The article aims to compare receptor mechanisms related to neurotransmitters for some of the most widely used psychoactive substances - amphetamine, cocaine, ecstasy (MDMA), and psilocybin - and to link these mechanisms to cardiovascular effects, thermoregulation, and neurotoxicity. The review is based mainly on in vitro studies on transporters and receptors, animal models, and controlled clinical trials in humans. Amphetamine is a substrate for NET/DAT and VMAT2, inducing reverse monoamine transport and their release into the synapse, particularly norepinephrine and dopamine, leading to subsequent sympathomimetic effects and oxidative stress. Cocaine acts primarily as an inhibitor of monoamine reuptake via DAT/NET/SERT, with similar affinity for all three, which markedly increases DA/NA/5-HT levels and is associated with a high risk of cardiotoxicity. MDMA combines releasing and reuptake-inhibiting properties, with preference for SERT/NET, producing strong 5-HT efflux and empathogenic effects, but also hyperthermia, cardiovascular disturbances, and, in animal models, persistent serotonergic neurotoxicity involving oxidative stress and glutamate-mediated excitotoxicity. Psilocybin (psilocin) acts mainly as a 5-HT_{2A} agonist, with contributions from 5-HT_{1A/2C} receptors and neurotrophin receptors, promoting neuroplasticity and beneficial behavioral effects with relatively low acute somatic toxicity and moderate, transient hemodynamic changes in healthy volunteers. Overall, although all substances modulate the monoaminergic system, psychostimulants carry substantially higher cardiovascular and neurotoxic risk than psilocybin, which shows a favorable safety profile under controlled conditions.

KEYWORDS

Cocaine, Amphetamine, Ecstasy, Psilocybin, Neurotoxicity

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Introduction

Psychoactive substances are defined as all chemical compounds acting on the central nervous system that can induce changes in perception, mood, consciousness, and behaviour. Amphetamine and cocaine are classical activating agents - stimulants, 3,4-methylenedioxymethamphetamine (MDMA) combines stimulant and „entactogenic” properties, whereas psilocybin is a psychedelic with pronounced neuroplastic effects [1] [2]. The aim of this article is to compare their mechanisms of action and associated psychological and physical effects.

Methodology

The review is based on both review and experimental studies on the pharmacology of amphetamine and other stimulants, articles on the pharmacology and toxicity of MDMA, including preclinical data and human neuroimaging, studies on the mechanisms of action of psilocybin and other serotonergic psychedelics, and work on monoaminergic mechanisms and the reward system that are also relevant to cocaine.

Results

1. Primary mechanisms of action

Psychostimulants

Amphetamine and cocaine are psychostimulants that act predominantly on the monoaminergic system (DA - dopamine, NA - noradrenaline, 5-HT - serotonin). The main differences in their effects concern the mode of interaction with monoamine transporters (DAT - dopamine transporter, NET - noradrenaline transporter, SERT - serotonin transporter), synaptic vesicles, and intracellular receptors [1] [2] [3].

Amphetamine does not act by directly stimulating adrenergic receptors (as adrenaline or noradrenaline do), but by modifying the handling of endogenous neurotransmitters - noradrenaline and dopamine. Amphetamine is a substrate for the monoamine transporters NET and DAT. After entering the neuron, it is transported into synaptic vesicles via the vesicular transporter VMAT2, where it displaces stored NA and DA into the neuronal cytosol, markedly increasing their intracellular concentration [3] [4]. The high cytoplasmic catecholamine level causes membrane transporters (DAT/NET) to reverse their direction of action. Instead of taking up neurotransmitters from the synaptic cleft into the neuron, they begin to expel them from the cytoplasm into the synaptic cleft. In summary, amphetamine enhances DA and NA activity through reverse transport via DAT/NET and modulation of VMAT2. It acts most strongly at NET, less at DAT, and only weakly at SERT [1].

Cocaine is not a receptor agonist in the sense of directly stimulating receptors. Its key mechanism is inhibition of monoamine reuptake. Cocaine binds to DAT, NET, and SERT on the presynaptic membrane, leading to their blockade. This prevents removal of neurotransmitters from the synaptic cleft back into the neuron. In addition, cocaine blocks sodium channels, which underlies its local anaesthetic effects by stabilizing cell membranes. In summary, cocaine acts by blocking monoamine reuptake at NET/DAT/SERT, thereby enhancing DA/NA/5-HT neurotransmission [8] [9]. It exhibits similar potency at DAT, NET, and SERT, with K_i values of approximately 0.2–0.7 μM , meaning that very low concentrations near synapses are sufficient to effectively block transporters and increase dopamine, noradrenaline, and serotonin levels in the synaptic cleft. The lower the K_i , the higher the affinity for a given target [9] [10].

MDMA

MDMA is an amphetamine derivative with potent serotonergic activity: it stimulates 5-HT release via SERT and, to a lesser extent, DA. It produces a mixed stimulant and psychedelic profile, inducing empathy, euphoria and pronounced entactogenic effects. MDMA enters the neuron through SERT, displaces 5-HT from vesicles via VMAT2, increases its cytoplasmic concentration, and subsequently induces a strong, non-vesicular reverse transport through SERT, resulting in a massive 5-HT efflux in human transporters it produces a markedly greater efflux of 5-HT than of DA or NE, despite similar affinities for the respective transporters. Its selective action on 5-HT is driven not only by affinity for SERT, but by a higher efficacy in inducing efflux, i.e. exchange of intracellular 5-HT to the extracellular space via the same transporter that normally mediates its reuptake [12].

Psilocybin

Psilocybin is a prodrug - its active metabolite psilocin acts as an agonist at serotonin receptors, particularly 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1A}. In humans, the intensity of psychedelic experiences correlates with 5-HT_{2A} occupancy (up to 72%) and plasma psilocin concentrations. Psilocybin promotes neuroplasticity by increasing dendritic spine density in the cortex and strengthening excitatory synapses, with behavioral and structural effects depending on 5-HT_{2A} receptors in specific pyramidal neuron subtypes. Its actions extend beyond 5-HT_{2A}, involving 5-HT_{1A}/2C as well as neurotrophin receptors (e.g. TrkB), which underlie long-lasting remodeling of neural networks [14].

2. Physical effects

Cardiovascular system and thermoregulation

Amphetamine, cocaine and MDMA, by intensifying NA/DA/5-HT transmission, cause tachycardia, increased blood pressure, arrhythmia, as well as cardiovascular and thermoregulatory complications (hyperthermia) [2] [3] [4]. Sympathomimetic toxidrome symptoms may occur when using psychostimulants: moist, „sweaty" skin, tachycardia, hypertension, mydriasis, psychomotor agitation, muscle tremor, and hyperthermia. Regarding MDMA, in controlled studies in healthy individuals, 75–125 mg of MDMA often caused: systolic blood pressure >160

mmHg (33%), heart rate >100/min (29%), and temperature >38°C (19%) [11]. Psilocybin induces moderate sympathetic activation: a transient increase in blood pressure and heart rate, with a generally good safety profile in cardiologically healthy individuals. In clinical studies in healthy volunteers, psilocybin moderately increased blood pressure and heart rate, the effect is transient and assessed as „cardiostimulant but well tolerated." A meta-analysis of 10 studies showed an increase in SBP of approximately 19 mmHg and DBP of approximately 8.7 mmHg, and heart rate was comparable to placebo [14].

Neurotoxicity

Amphetamine induces large, transporter-dependent burst catecholamine release, the formation of reactive oxygen and nitrogen species, and transporter modifications (phosphorylation, altered trafficking), which are associated with DA neurotoxicity and neurodegenerative disorders [2] [9]. Cocaine administered during adolescence in animals causes cognitive deficits, anxiety, and reduced synaptic and dendritic spine density in the prefrontal cortex in adulthood, suggesting long-term neurotoxic damage [1].

Mechanisms of MDMA neurotoxicity include oxidative stress (free radicals from metabolites), MAO-dependent DA/5-HT metabolism, formation of reactive oxygen species, glutamatergic excitotoxicity, and aggregation of hyperthermia with other factors [16]. Glutamatergic cytotoxicity is the result of a chain of events: MDMA causes 5-HT release, 5-HT_{2A/C} activation, and a subsequent increase in glutamate (facilitated by COX/prostaglandins). This results in excessive activation of glutamate receptors on vulnerable neurons, which may cause their damage or degeneration. Long-term MDMA exposure induces selective degeneration of serotonergic axonal terminals in rats and monkeys, persisting for months or even years [17]. MDMA studies demonstrate pronounced neurotoxicity in animal brains, particularly in the serotonin system and, in some models, also in the dopamine system. In humans, long-term changes in serotonin markers and cognitive function are evident, but their irreversibility and magnitude remain unclear. Reviews and meta-analyses indicate reduced serotonin transporter (SERT) density in numerous brain regions in heavy MDMA users, with partial normalization after prolonged abstinence [12].

In clinical studies, psilocybin is characterized by relatively low acute somatic toxicity [18]. In healthy volunteers, the intensity of psychedelic experiences (alterations in perception, thinking, and emotions) closely correlates with 5-HT_{2A} occupancy and plasma psilocin levels [19]. In mice, psilocybin reverses anhedonia in models of depression and enhances excitatory synapses in the hippocampus. These effects may be independent of 5-HT_{2A}, suggesting the possibility of separating antidepressant from hallucinogenic effects. Psilocybin improves cognitive flexibility in complex reinforcement learning tasks and may reduce anorexic behaviors via 5-HT_{1A} and 5-HT_{2A} receptors [20].

Discussion

The substances analyzed here act primarily by modulating monoaminergic systems, but differ in their receptor profile, duration of action, and toxicity. Amphetamine and cocaine strongly activate the reward system by increasing DA in the nucleus accumbens, while simultaneously enhancing NA and 5-HT, which is responsible for sympathomimetic effects and cardiovascular complications [1][2][3]. MDMA combines amphetamine-like mechanisms with a dominant effect on 5-HT, which translates into empathogenic effects, but also into selective serotonergic neurotoxicity, especially with repeated exposure and under conditions promoting hyperthermia [1] [12]. Psilocybin acts primarily through 5-HT_{2A}, but also other receptor subtypes and neurotrophin receptors, promoting rapid and sustained neuroplasticity in the cortex and limbic structures [14]. Preclinical studies indicate that antidepressant and procognitive effects may be partially independent of full hallucinogenic effects (e.g., lack of complete blockade of antianhedonic effects after 5-HT_{2A} antagonism) [19] [20]. From a clinical perspective, clinical heterogeneity is clearly visible: stimulants (amphetamine, cocaine, MDMA in recreational doses) are characterized by a high risk of addiction, neurotoxicity, and organ damage, while psilocybin, with controlled administration demonstrates a favorable safety profile and therapeutic potential, although longterm safety requires further studies [21]. Research on MDMA in therapy (e.g., PTSD) and psilocybin in depression, anxiety, and eating disorders indicates that modulation of the same systems that lead to toxicity after abuse, under carefully controlled conditions, can be a source of significant clinical benefits. Therefore, dose, frequency of use, context (medical vs. recreational), and individual factors (genetics, comorbidities) are crucial [22].

Conclusions

Amphetamine, cocaine, MDMA, and psilocybin interfere with the same fundamental neurotransmitter systems, but their receptor profiles and dynamics of action generate distinct somatic and psychological risks. Psychostimulants are the primary culprits of neurotoxicity, cardiovascular complications, and addiction, while psilocybin is distinguished by its low acute toxicity and pronounced neuroplastic potential, which forms the basis for its therapeutic applications. The diversity of effects with similar molecular targets emphasizes the need for precise assessment of dose, regimen, and individual patient sensitivity when considering both the risks and possible clinical applications of these substances.

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REFERENCES

1. Docherty J.R., Alsufyani H. Pharmacology of Drugs Used as Stimulants. *Journal of Clinical Pharmacology*. 2021;61(8):1063–1079. <https://doi.org/10.1002/jcph.1859>.
2. Rothman R.B., Baumann M.H. Monoamine transporters and psychostimulant drugs. *European Journal of Pharmacology*. 2003;479(1–3):23–40. <https://doi.org/10.1016/j.ejphar.2003.08.054>.
3. Sitte H.H., Freissmuth M. Amphetamines, new psychoactive drugs and the monoamine transporter cycle. *Trends in Pharmacological Sciences*. 2015;36(1):41–50. <https://doi.org/10.1016/j.tips.2014.11.006>.
4. Støier J.F., Konomi-Pilkati A., Apuschkin M., Herborg F., Gether U. (2023). Amphetamine-induced reverse transport of dopamine does not require cytosolic Ca^{2+} . *The Journal of Biological Chemistry*, 299(8): 104939. <https://doi.org/10.1016/j.jbc.2023.104939>.
5. Jones S.R., Gainetdinov R.R., Wightman R.M., Caron M.G. (1998). Mechanisms of Amphetamine Action Revealed in Mice Lacking the Dopamine Transporter. *The Journal of Neuroscience*, 18(6):1979–1986. <https://doi.org/10.1523/JNEUROSCI.18-06-01979.1998>.
6. Eiden L.E., Weihe E. (2011). VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. *Annals of the New York Academy of Sciences*, 1216(1):86–98. <https://doi.org/10.1111/j.1749-6632.2010.05906.x>.
7. Robertson S.D., Matthies H.J.G., Galli A. (2009). A closer look at amphetamine induced reverse transport and trafficking of the dopamine and norepinephrine transporters. *Molecular Neurobiology*, 39(2):73–80. <https://doi.org/10.1007/s12035-009-8053-4>.
8. Shaili Aggarwal, Ole Mortensen (2017). Overview of Monoamine Transporters. *Current Protocols in Pharmacology*, 79(1): 12.16.1–12.16.17. <https://doi.org/10.1002/cpph.30>.
9. Dawn D. Han, Howard H. Gu (2006). Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. *BMC Pharmacology*, 6:6. <https://doi.org/10.1186/1471-2210-6-6>.
10. James Eshleman, Melissa Carmolli, Michael Cumbay, Carey R. Martens, Kevin A. Neve, Aaron Janowsky (1999). Characteristics of drug interactions with recombinant biogenic amine transporters expressed in the same cell type. *The Journal of Pharmacology and Experimental Therapeutics*, 289(2):877–885.

11. Catherine Verrico, Gerald Miller, Bertha K. Madras, 2007, "MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment", *Psychopharmacology*, Berlin: Springer. <https://doi.org/10.1007/s00213-006-0555-9>
12. Gary Rudnick, Stephen C. Wall, 1992, "The molecular mechanism of 'ecstasy' [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release", *Proceedings of the National Academy of Sciences of the USA*, Washington (DC): National Academy of Sciences. <https://doi.org/10.1073/pnas.89.5.1817>
13. Larraitz Lizarraga, Aram B. Cholanians, Andy V. Phan, Joseph M. Herndon, Stephen S. Lau, Terrence A. Monks, 2014, "Vesicular monoamine transporter 2 and the acute and long-term response to 3,4-(±)-methylenedioxymethamphetamine", *Toxicological Sciences*, Oxford: Oxford University Press. <https://doi.org/10.1093/toxsci/kfu238>
14. [Sonia Sonda, Diana Pendin, Silvia Comai, Sara De Martin, Paolo L. Manfredi, Andrea Mattarei, 2025, Emerging mechanisms of psilocybin-induced neuroplasticity, *Trends in Pharmacological Sciences*, Amsterdam: Elsevier. <https://doi.org/10.1016/j.tips.2024.07.004>
15. Makiath Adebo, Marie Bonnet, Ons Laouej, Claire Defaix, Josephine C. McGowan, Florence Butlen-Ducuing, David David, Erwan Poupon, Lucile Tritschler, Alain M. Gardier, 2025, Psilocybin as Transformative Fast-Acting Antidepressant: Pharmacological Properties and Molecular Mechanisms, *Fundamental & Clinical Pharmacology*, Oxford: Wiley. <https://doi.org/10.1111/fcp.13102>
16. João Paulo Capela, Helena Carmo, Fátima Remião, Maria de Lourdes Bastos, Alexander Meisel, Félix Carvalho, 2009, *Molecular and Cellular Mechanisms of Ecstasy-Induced Neurotoxicity: An Overview*, Molecular Neurobiology, New York: Springer. <https://doi.org/10.1007/s12035-009-8064-1>
17. Desislava Popova, Andréas N. P. Forsblad, Sanaz Hashemian, Sven Ove Jacobsson, 2016, Non-Serotonergic Neurotoxicity by MDMA (Ecstasy) in Neurons Derived from Mouse P19 Embryonal Carcinoma Cells, *PLOS ONE*, San Francisco: Public Library of Science. <https://doi.org/10.1371/journal.pone.0166750>
18. Friederike Holze, Lisa Ley, Friederike Müller, Anna M. Becker, Isabelle Straumann, Patrick Vizeli, Sven Kuehne, Mads A. Røder, Urs Duthaler, Karolina E. Kolaczynska, Neha Varghese, Andrea Eckert, Matthias E. Liechti, 2022, „Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects”, *Neuropsychopharmacology*, London: Nature Publishing Group, <https://doi.org/10.1038/s41386-021-01252-6>.
19. Martin K. Madsen, Patrick M. Fisher, Daniel Burmester, Agnete Dyssegaard, Dea S. Stenbæk, Sara Kristiansen, Sys S. Johansen, Sczabolcs Lehel, Kristian Linnet, Claus Svarer, David Erritzoe, Brice Ozenne, Gitte M. Knudsen, 2019, „Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels”, *Neuropsychopharmacology*, London: Nature Publishing Group, <https://doi.org/10.1038/s41386-018-0277-9>.
20. Natalie Hesselgrave, Timothy A. Troppoli, Andreas B. Wulff, Anthony B. Cole, Scott M. Thompson, 2021, „Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice”, *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, Washington (DC): National Academy of Sciences, <https://doi.org/10.1073/pnas.2022489118>.
21. Rosario Moratalla, Amit Khairnar, Nicola Simola, Noemí Granado, José-Rubén García-Montes, Pier Francesca Porceddu, Yousef Tizabi, Giulia Costa, Monica Morelli, 2017, "Amphetamine-related drugs neurotoxicity in humans and in experimental animals: Main mechanisms", *Progress in Neurobiology*, Amsterdam: Elsevier, <https://doi.org/10.1016/j.pneurobio.2016.10.007>.
22. Jennifer M. Mitchell, Michael P. Bogenschutz, Alia Lilienstein, Candice Harrison, Sarah E. Kleiman i in., 2021, „MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study”, *Nature Medicine*, New York, NY: Springer Nature, <https://doi.org/10.1038/s41591-021-01336-3>