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Editorial

Pharmacology and Toxicology of Amphetamine-Type Stimulants

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Amphetamine-type stimulants are drugs chemically related to the natural compounds ephedrine and cathinone [1]. Their chemical structure has a phenylethylamine moiety, which resembles the monoamine neurotransmitters, dopamine, noradrenaline and serotonin (also known as 5-hydroxitryptamine) [2].

Amphetamines target the brain and their pharmacological mechanism of action is mainly related to their ability to serve as substrates of monoamine transporters. They increase the concentration of monoamines in the synaptic cleft [2]. Still, the full comprehension of their brain mechanisms remains to be established, with research continuing today.

The first amphetamine was discovered more than a century ago, and thereafter they have been used in clinical settings for treating depression, obesity and nasal congestion. However, these clinical uses are nowadays considered obsolete in developed countries [3]. Notwithstanding, amphetamine and methylphenidate are currently first-line therapies for attention-deficit/hyperactivity disorder (ADHD) [4], and they are also used in the treatment of narcolepsy [5]. Meanwhile, new clinical uses are being considered for these drugs. 3,4-Methylenedioxymethamphetamine ("ecstasy", or MDMA)-assisted psychotherapy is being studied for the treatment of post-traumatic stress disorder (PTSD) [6,7], and even the emergence of psychedelics for treating depression seems to bring "ecstasy" to the table [8,9]. These new uses clearly show that much remains to be discovered regarding the brain actions of these drugs.

Amphetamines moved from the clinics to the streets and became major worldwide drugs of abuse. According the World Drug Report 2021 of the United Nations, in 2019, there were an estimated 27 million past-year users of amphetamines, including amphetamine and methamphetamine, corresponding to 0.5 per cent of the global population aged 15–64 [10]. In addition, nearly 20 million people globally are estimated to have used "ecstasy" in the past year, corresponding to 0.4 per cent of the global population aged 15–64 [10]. There have been many concerns surrounding the misuse of amphetamines given the toxicity reported in drug abusers, namely neurotoxicity, cardiotoxicity and hepatotoxicity, which have been widely studied in pre-clinical settings [1,11–13]. However, the mechanisms of toxicity are far from being fully understood and the recent advances towards the potential clinical uses of amphetamines render the investigations of toxicity mechanisms even more important.

It is unknown how amphetamine-type stimulants will be used in future, but it is likely that new answers, clinical repurposing of old drugs and the development of new and safer amphetamines will arise. This topic aims to bring together the latest findings in the field of amphetamine-type stimulants, from in vitro to pre-clinical studies or even clinical studies to identify novel mechanisms underlying their (neuro)pharmacology and toxicology, but also new targets for novel clinical uses. We aim to bring new data and novel ideas to our readers in order to contribute to the development of this exciting field of research.

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References

1. Carvalho, M.; Carmo, H.; Costa, V.M.; Capela, J.P.; Pontes, H.; Remião, F.; Carvalho, F.; Bastos Mde, L. Toxicity of amphetamines: An update. *Arch. Toxicol.* **2012**, *86*, 1167–1231. [CrossRef] [PubMed]
2. Sitte, H.H.; Freissmuth, M. Amphetamines, new psychoactive drugs and the monoamine transporter cycle. *Trends Pharmacol. Sci.* **2015**, *36*, 41–50. [CrossRef] [PubMed]
3. Heal, D.J.; Smith, S.L.; Gosden, J.; Nutt, D.J. Amphetamine, past and present—A pharmacological and clinical perspective. *J. Psychopharmacol.* **2013**, *27*, 479–496. [CrossRef] [PubMed]
4. Wolraich, M.; Brown, L.; Brown, R.T.; DuPaul, G.; Earls, M.; Feldman, H.M.; Ganiats, T.G.; Kaplanek, B.; Meyer, B.; Perrin, J.; et al. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* **2011**, *128*, 1007–1022. [CrossRef] [PubMed]
5. Thorpy, M.J.; Dauvilliers, Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med.* **2015**, *16*, 9–18. [CrossRef] [PubMed]
6. Yazar-Klosinski, B.; Mithoefer, M. Potential Psychiatric Uses for MDMA. *Clin. Pharmacol. Ther.* **2017**, *101*, 194–196. [CrossRef] [PubMed]
7. Mitchell, J.M.; Bogenschutz, M.; Lilienstein, A.; Harrison, C.; Kleiman, S.; Parker-Guilbert, K.; Ot'alora, G.M.; Garas, W.; Paleos, C.; Gorman, I.; et al. MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. *Nat. Med.* **2021**, *27*, 1025–1033. [CrossRef] [PubMed]
8. Vargas, M.V.; Dunlap, L.E.; Dong, C.; Carter, S.J.; Tombari, R.J.; Jami, S.A.; Cameron, L.P.; Patel, S.D.; Hennessey, J.J.; Saeger, H.N.; et al. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science* **2023**, *379*, 700–706. [CrossRef] [PubMed]
9. Katsnelson, A. How MDMA resensitizes the brain. *Nature* **2022**, *609*, S86. [CrossRef] [PubMed]
10. UNODC. *World Drug Report 2021*; United Nations Publication: Vienna, Austria, 2021.
11. Capela, J.P.; Carmo, H.; Remião, F.; Bastos, M.L.; Meisel, A.; Carvalho, F. Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: An overview. *Mol. Neurobiol.* **2009**, *39*, 210–271. [CrossRef] [PubMed]
12. Capela, J.P.; Carvalho, F.D. A review on the mitochondrial toxicity of "ecstasy" (3,4-methylenedioxymethamphetamine, MDMA). *Curr. Res. Toxicol.* **2022**, *3*, 100075. [CrossRef] [PubMed]
13. Richards, J.R.; Albertson, T.E.; Derlet, R.W.; Lange, R.A.; Olson, K.R.; Horowitz, B.Z. Treatment of toxicity from amphetamines, related derivatives, and analogues: A systematic clinical review. *Drug Alcohol Depend.* **2015**, *150*, 1–13. [CrossRef] [PubMed]