

Review article

Molecular and clinical aspects of potential neurotoxicity induced by new psychoactive stimulants and psychedelics

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ARTICLE INFO

Keywords:

New psychoactive substance
Neurotoxicity
Stimulant
Psychedelic
Serotonin
Dopamine

ABSTRACT

New psychoactive stimulants and psychedelics continue to play an important role on the illicit new psychoactive substance (NPS) market. Designer stimulants and psychedelics both affect monoaminergic systems, although by different mechanisms. Stimulant NPS primarily interact with monoamine transporters, either as inhibitors or as substrates. Psychedelic NPS most potently interact with serotonergic receptors and mediate their mind-altering effects mainly through agonism at serotonin 5-hydroxytryptamine-2A (5-HT_{2A}) receptors. Rarely, designer stimulants and psychedelics are associated with potentially severe adverse effects. However, due to the high number of emerging NPS, it is not possible to investigate the toxicity of each individual substance in detail. The brain is an organ particularly sensitive to substance-induced toxicity due to its high metabolic activity. In fact, stimulant and psychedelic NPS have been linked to neurological and cognitive impairments. Furthermore, studies using in vitro cell models or rodents indicate a variety of mechanisms that could potentially lead to neurotoxic damage in NPS users. Cytotoxicity, mitochondrial dysfunction, and oxidative stress may potentially contribute to neurotoxicity of stimulant NPS in addition to altered neurochemistry. Serotonin 5-HT_{2A} receptor-mediated toxicity, oxidative stress, and activation of mitochondrial apoptosis pathways could contribute to neurotoxicity of some psychedelic NPS. However, it remains unclear how well the current preclinical data of NPS-induced neurotoxicity translate to humans.

1. Introduction

New psychoactive substances (NPS) with stimulant and psychedelic properties include a rich number of compounds that shape the illicit designer drug market together with synthetic cannabinoids, synthetic opioids, and dissociatives. NPS are synthetic drugs derived from clandestine modification of traditional drugs of abuse, with a similar pharmacological profile. Various of such substances originate from industrial or academic research but later appeared on the recreational drug market, often remaining outside of legal control. The principal mechanisms of action of NPS overlap with traditional drugs of abuse. Stimulant and psychedelic NPS both mediate their psychoactive effects by interacting with monoaminergic targets. Stimulant NPS act as inhibitors or substrates of norepinephrine, dopamine, and serotonin (5-HT) transporters (NET, DAT, and SERT, respectively) (Fleckenstein et al., 2000; Luethi and Liechti, 2020; Rothman and Baumann, 2003; Sitte and Freissmuth, 2015). Psychedelics primarily activate 5-hydroxytryptamine (5-HT)

type 2 receptors as partial or full agonists (Luethi and Liechti, 2020; Nichols, 2016). In addition to these main mechanisms of action, stimulant and psychedelic NPS interact with other monoaminergic targets. Different NPS display diverse selectivity towards various targets, which combined with their respective pharmacokinetics result in qualitative differences between the drugs. NPS use may potentially result in severe central and peripheral adverse effects and even death. However, due to the novelty of NPS and a lack of clinical studies, NPS-associated adverse effects are often only poorly investigated. The brain is particularly sensitive to toxicity due to its high metabolic activity and its limited ability to regenerate. The high energy demand in the form of glucose originates from energy-consuming neuronal functions, such as synaptic transmissions and axonal transport. Neurogenesis is limited to certain areas of the adult brain, but the existing neurons do not divide further (Gage, 2002). Hence, toxicity leading to neuronal dysfunction or even cell death may result in irreversible damage depending on the affected brain area.

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<https://doi.org/10.1016/j.expneurol.2021.113778>

Received 11 February 2021; Received in revised form 25 May 2021; Accepted 29 May 2021

Available online 4 June 2021

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Potential neurotoxic effects of NPS can be expected due to increased neurotransmitter levels, enhanced functional activity at the respective receptors, or direct cellular toxicity leading to mitochondrial dysfunction, apoptosis, or inhibition of neurogenesis. The primary mechanism of action of NPS is nowadays relatively well described. Additionally, a variety of in vitro and in vivo studies suggests an additional “off-target” neurotoxic potential for several compounds. Furthermore, the pharmacological similarity of some NPS to traditional drugs with known neurotoxic potential suggests that such NPS may be neurotoxic as well. With this review, we aim to provide an overview over the possible neurological consequences associated with stimulant and psychedelic NPS and describe their pharmacology as well as potential molecular mechanisms of neurotoxicity.

2. Methodology

2.1. Terminology

NPS-induced neurotoxicity was defined as adverse effects on the function or structure of the central or peripheral nervous system that directly resulted from the pharmacological activity of an NPS. Neurological sequelae or neurological consequence was defined as structural, physiological, psychological, or behavioral change, either directly or indirectly linked to the mechanism of action of an NPS.

2.2. Substance classes

The focus of this review are NPS that primarily mediate their psychoactive effects through monoaminergic systems. Monoaminergic NPS can be further divided into stimulants that mainly mediate their effects via monoamine transporter interactions and psychedelics that display agonist activity at serotonergic receptors. Stimulant NPS of the following substance classes were included in this review: amphetamines, cathinones including pyrovalerone derivatives, benzofurans, indoles, aminoindanes, piperazines, phenidates, aminorex derivatives, phenmetrazine derivatives, and thiophenes. Psychedelic NPS of the following substance classes were included in this review: phenethylamines including *N*-benzylmethoxy-substituted (“NBOMe”) derivatives, tryptamines, and lysergamides.

2.3. Search strategy

The following key words were searched in PubMed and the amount of results is indicated in brackets: “amphetamine + NPS + toxicity” (56); “amphetamine + designer drug + toxicity” (201); “amphetamine + NPS + pharmacology” (113); “amphetamine + designer drug + pharmacology” (578); “cathinone + NPS + toxicity” (54); “cathinone + designer drug + toxicity” (117); “cathinone + NPS + pharmacology” (94); “cathinone + designer drug + pharmacology” (272); “pyrovalerone” (71); “benzofuran + NPS” (63); “benzofuran + designer drug” (28); “indole + NPS + toxicity” (113); “indole + designer drug + toxicity” (61); “indole + NPS + pharmacology” (334); “indole + designer drug + pharmacology” (173); “aminoindane” (129); “piperazine + NPS” (129); “phenidate” (36); “methylphenidate + NPS” (32); “methylphenidate + designer drug” (19); “aminorex” (163); “phenmetrazine + NPS” (7); “phenmetrazine + designer drug” (6); “thiophene + NPS” (102); “thiophene + designer drug” (7); “psychedelic + phenethylamine + NPS + toxicity” (18); “psychedelic + phenethylamine + designer drug + toxicity” (105); “psychedelic + phenethylamine + NPS + pharmacology” (34); “psychedelic + phenethylamine + designer drug + pharmacology” (313); “NBOMe” (208); “tryptamine + NPS” (103); “tryptamine + designer drug” (160); “lysergamide” (77); “LSD + NPS” (41); “LSD + designer drug” (57).

In addition, the following key words were searched within the journal *Forensic Toxicology* (Springer) as it was not indexed in PubMed at the time of the study: “NPS + toxicity” (39) “designer drug + toxicity”

(55); “amphetamine + toxicity” (55); “cathinone + toxicity” (34); “benzofuran” (7); “indole + NPS”; “indole + designer drug” (39); “aminoindane” (2); “piperazine” (18); “phenidate” (0); “aminorex” (2); “phenmetrazine” (0); “thiophene” (8); “phenethylamine” (51); “tryptamine” (16); “lysergamide” (0).

3. Stimulant NPS

Stimulant NPS modulate monoaminergic neurotransmission either as monoamine transporter inhibitors or as transporter substrates that mediate non-exocytotic substrate efflux (Fleckenstein et al., 2000; Rothman and Baumann, 2003; Sitte and Freissmuth, 2015). In addition, various stimulant NPS interact with monoaminergic receptors, including adrenergic, dopaminergic, and serotonergic receptors, and with trace amine-associated receptor 1 (TAAR1) (Luethi and Liechti, 2020; Simmler et al., 2016). Stimulant NPS may furthermore display substrate activity at vesicular monoamine transporters (VMATs) and inhibit monoamine oxidases (Fleckenstein et al., 2007; Partilla et al., 2006; Sitte and Freissmuth, 2015; Volz et al., 2007). Besides different mechanisms of action (i.e., transporter inhibition vs. substrate activity), individual stimulant NPS mainly differ regarding their selectivity to one over another transporter (Luethi and Liechti, 2018, 2020). Distinct dopaminergic activity is associated with greater stimulant-type reinforcing effects and increased abuse liability (Kuhar et al., 1991; Ritz et al., 1987; Wee et al., 2005; Wee and Woolverton, 2006). In contrast, serotonergic activity is linked to an entactogenic, 3,4-methylenedioxyamphetamine (MDMA)-like acute effect profile and lower abuse liability (Baumann et al., 2000; Suyama et al., 2019; Suyama et al., 2016). Stimulant NPS comprise several drug classes including amphetamines, cathinones (β -keto-amphetamines), benzofurans, indoles, aminoindanes, piperazines, thiophenes, phenidates, aminorex derivatives, and phenmetrazine derivatives (Luethi and Liechti, 2020). The noradrenergic, dopaminergic, and serotonergic selectivity may vary distinctively among substances of a drug class, depending on the chemical structure. Compared to the amount of research regarding traditional stimulants, such as amphetamine, cocaine, and MDMA, there is currently relatively little information on neurotoxicity of stimulant NPS available. However, several in vitro and in vivo studies suggest a neurotoxic potential for some stimulant NPS. Additionally, a detailed understanding of the mechanism of action of the individual NPS helps evaluating potential neurological consequences and the risk of neurotoxicity.

3.1. Pharmacology of stimulant NPS

3.1.1. Monoamine transporter selectivity of stimulants

The pharmacological profile of stimulant NPS not only allows to make predictions about the acute subjective effects but also predictions about mechanisms that could potentially lead to toxicity. Virtually all used stimulant NPS potently interact with NET, which together with DAT interactions determines the clinical potency of the substances (i.e., the amount or concentration of substance needed to induce psychoactivity) (Luethi and Liechti, 2018). The subjective effect differences between the individual stimulants are largely driven by different relative selectivity towards DAT over SERT. Stimulants with a high (>10-fold) DAT vs. SERT selectivity elicit distinct psychostimulant effects and are associated with a high abuse potential (Kuhar et al., 1991; Ritz et al., 1987; Wee et al., 2005; Wee and Woolverton, 2006). Stimulants with a high (>10-fold) SERT vs. DAT selectivity are likely to produce entactogenic effects and are associated with a relatively low abuse liability (Baumann et al., 2000; Suyama et al., 2019; Suyama et al., 2016). The DAT vs. SERT selectivity of a variety of stimulant-type NPS and traditional stimulants is shown in Table 1 and Fig. 1. The corresponding pharmacological profiles have been assessed by identical methodology in transporter-transfected human embryonic kidney (HEK) 293 cells. The precise assessment of the monoamine transporter selectivity for newly emerged stimulants and the inclusion of appropriate controls aids

Table 1
DAT vs. SERT selectivity of a variety of stimulants.

| Substance | Abbreviation | DAT/SERT ratio | Source of pharmacological data |
|--|-------------------|----------------|--------------------------------|
| 5-Methoxy-6-methyl-2-aminoindane | MMAI | 0.004 | Luethi et al. (2018c) |
| 5-(2-Aminopropyl)-2,3-dihydrobenzofuran | 5-APDB | 0.010 | Rickli et al. (2015b) |
| 5-(2-Methylaminopropyl)-2,3-dihydrobenzofuran | 5-MAPDB | 0.020 | Rickli et al. (2015b) |
| 2,4-Dimethylmethcathinone | 2,4-DMMC | 0.020 | Luethi et al. (2018c) |
| 4-Methylthioamphetamine | 4-MTA | 0.020 | Simmler et al. (2014a) |
| <i>para</i> -Methoxyamphetamine/4-methoxyamphetamine | PMA | 0.030 | Simmler et al. (2014a) |
| <i>meta</i> -Chlorophenylpiperazine | <i>m</i> -CPP | 0.039 | Simmler et al. (2014b) |
| <i>para</i> -Methoxy- <i>N</i> -methylamphetamine | PMMA | 0.040 | Simmler et al. (2014a) |
| 5-(2-Aminopropyl)benzofuran | 5-APB | 0.050 | Rickli et al. (2015b) |
| 6-(2-Aminopropyl)-2,3-dihydrobenzofuran | 6-APDB | 0.070 | Rickli et al. (2015b) |
| 3,4-Methylenedioxy-methamphetamine | MDMA | 0.080 | Simmler et al. (2013) |
| <i>N</i> -methyl-1,3-benzodioxolyl-butanamine | MBDB | 0.090 | Simmler et al. (2013) |
| 5-Iodo-2-aminoindane | 5-IAI | 0.11 | Simmler et al. (2014b) |
| 3,4-Dimethylmethcathinone | 3,4-DMMC | 0.12 | Luethi et al. (2018c) |
| Methedrone/ <i>para</i> -methoxymethcathinone | | 0.14 | Simmler et al. (2014a) |
| 4-Ethylmethcathinone | 4-EMC | 0.14 | Rickli et al. (2015a) |
| 4-Chloroamphetamine/ <i>para</i> -chloroamphetamine | 4-CA/PCA | 0.14 | Luethi et al. (2019a) |
| 3,4-Methylenedioxy- <i>N</i> -ethylamphetamine | MDEA | 0.14 | Simmler et al. (2013) |
| 4-Methylamphetamine | 4-MA | 0.15 | Luethi et al. (2018c) |
| 5-(2-(Ethylaminopropyl)benzofuran | 5-EAPB | 0.15 | Rickli et al. (2015b) |
| 2,3-Dimethylmethcathinone | 2,3-DMMC | 0.16 | Luethi et al. (2018c) |
| 3,4-Methylenedioxyamphetamine | MDA | 0.24 | Rickli et al. (2015b) |
| 5,6-Methylenedioxy-2-aminoindane | MDAI | 0.27 | Simmler et al. (2014b) |
| 6-(2-Aminopropyl)benzofuran | 6-APB | 0.29 | Rickli et al. (2015b) |
| Brephedrone/4-bromomethcathinone | 4-BMC | 0.40 | Rickli et al. (2015a) |
| 4,4'-Dimethylaminorex | 4,4'-DMAR | 0.40 | Rickli et al. (2019) |
| Clephedrone/4-chloromethcathinone | 4-CMC | 0.45 | Luethi et al. (2019a) |
| 4-(2-Aminopropyl)benzofuran | 4-APB | 0.46 | Rickli et al. (2015b) |
| Mephedrone/4-methylmethcathinone | 4-MMC | 0.63 | Luethi et al. (2018c) |
| 7-(2-Aminopropyl)benzofuran | 7-APB | 0.65 | Rickli et al. (2015b) |
| Ethylone/3,4-methylenedioxy- <i>N</i> -ethcathinone | | 0.80 | Simmler et al. (2013) |
| 4-Fluoromethamphetamine | 4-FMA | 1.1 | Rickli et al. (2015a) |
| Diclofensine | | 1.1 | Luethi et al. (2018a) |
| 3,4-Methylenedioxycathinone | β -Keto-MDA | 1.5 | Rickli et al. (2015b) |
| <i>N</i> -ethylamphetamine | | 1.5 | Simmler et al. (2014a) |
| 4-Methylethcathinone | 4-MEC | 1.9 | Simmler et al. (2014a) |
| 5-(2-Aminopropyl)indole | 5-IT/5-API | 1.9 | Luethi et al. (2018c) |
| Naphyrone | | 2.0 | Simmler et al. (2013) |
| Butylone/ β -keto- <i>N</i> -methylbenzodioxolylbutanamine | | 2.1 | Simmler et al. (2013) |
| <i>N</i> -methyl-2-aminoindane | NM-2-AI | 2.5 | Luethi et al. (2018c) |
| Cocaine | | 3.1 | Simmler et al. (2013) |
| Methylone/3,4-methylenedioxy- <i>N</i> -methcathinone | | 3.3 | Simmler et al. (2013) |
| 1-Benzylpiperazine | BZP | 3.4 | Simmler et al. (2014b) |
| 4-Fluoroamphetamine/ <i>para</i> -fluoroamphetamine | 4-FA/PFA | 3.6 | Luethi et al. (2019a) |
| 3-Methylmethcathinone | 3-MMC | 3.7 | Luethi et al. (2018c) |
| Ethylphenidate | HDEP-28 | 5.0 | Luethi et al. (2018b) |
| Flephedrone/4-fluoromethcathinone | 4-FMC | 5.6 | Luethi et al. (2019a) |
| Pentylone/ β -keto-methylbenzodioxolylpentanamine | | 6.2 | Simmler et al. (2014a) |
| 4-Methylaminorex | 4-MAR | 7.2 | Rickli et al. (2019) |
| Ethcathinone | | 10 | Simmler et al. (2014a) |
| <i>d</i> -Methamphetamine | | 17 | Rickli et al. (2015a) |
| Amphetamine | | 30 | Luethi et al. (2019a) |
| Methcathinone | | 34 | Luethi et al. (2019a) |
| <i>N</i> -benzyl-ethylphenidate | <i>N</i> -Bn-EPH | 42 | Luethi et al. (2018b) |
| Diphenylprolinol | D2PM | 44 | Simmler et al. (2014b) |
| Propylphenidate | PPH | 70 | Luethi et al. (2018b) |
| 3,4-Dichloroethylphenidate | 3,4-DCEP | 100 | Luethi et al. (2018b) |
| 3',4'-Methylenedioxy- α -pyrrolidinobutyrophenone | MDPBP | 132 | Rickli et al. (2015a) |
| 3',4'-Methylenedioxy- α -pyrrolidinopropiophenone | MDPPP | 141 | Rickli et al. (2015a) |
| Methylmorphenate | | 141 | Luethi et al. (2018b) |
| Isopropylphenidate | IPH | 179 | Luethi et al. (2018b) |
| 3,4-Methylenedioxypropyvalerone | MDPV | 192 | Rickli et al. (2015a) |
| 3,4-Dichloromethylphenidate | 3,4-DCMP | 240 | Luethi et al. (2018b) |
| 4-Fluoromethylphenidate | 4F-MPH | 267 | Luethi et al. (2018b) |
| Pyrovalerone | | 327 | Rickli et al. (2015a) |
| Ethylphenidate | EPH | 421 | Luethi et al. (2018b) |
| 4-Methylmethylphenidate | 4-Me-MPH | 1093 | Luethi et al. (2018b) |
| Methylphenidate | MPH | 2108 | Luethi et al. (2018b) |

The DAT/SERT ratio is expressed as 1/DAT IC₅₀ : 1/SERT IC₅₀.

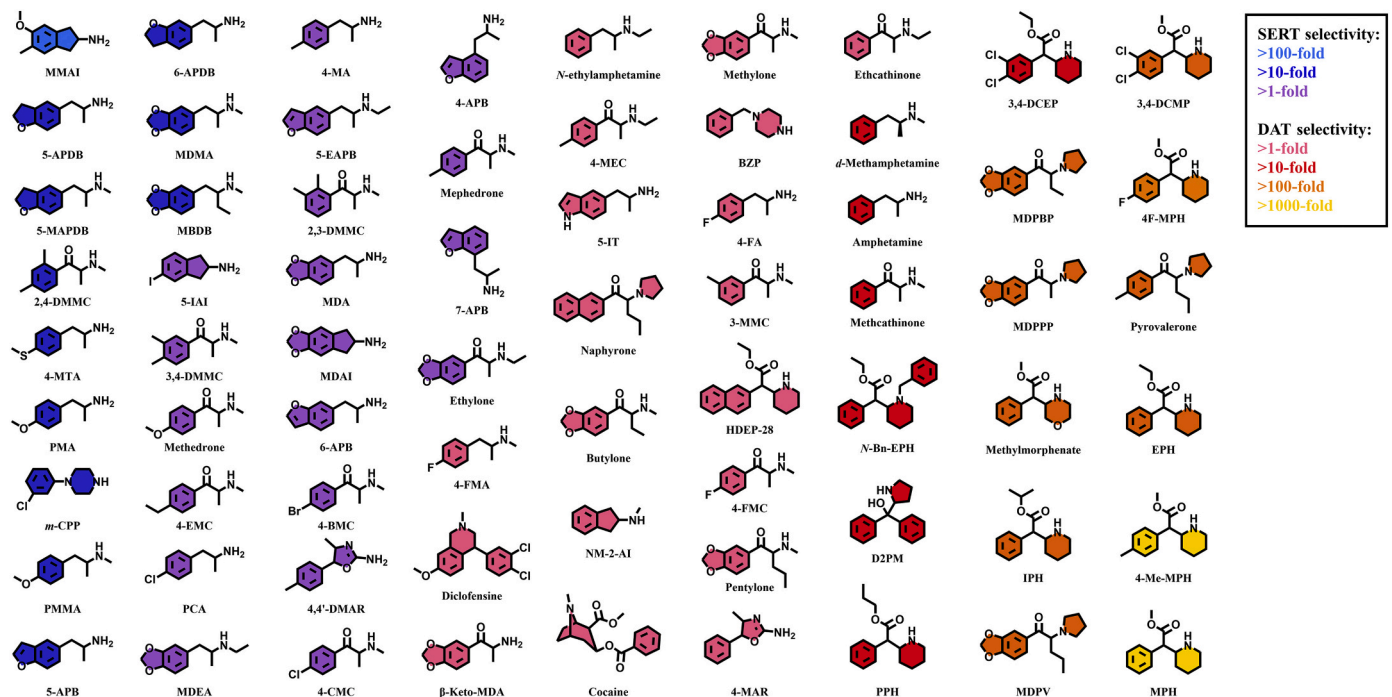


Fig. 1. Selectivity of stimulants for DAT or SERT. Stimulants with a high (>10) DAT/SERT ratio are associated with a high abuse potential. A low (<0.1) DAT/SERT ratio is linked to an entactogenic effect profile. The DAT/SERT ratio is expressed as $1/\text{DAT IC}_{50} : 1/\text{SERT IC}_{50}$.

evaluating the risk for addiction and toxicity (Ilic et al., 2020). In addition to distinctively serotonergic or dopaminergic substances, various stimulant NPS interact with DAT and SERT with relatively similar potency. Different stimulant NPS within a chemical class may display different selectivity towards different monoamine transporters, depending on the chemical substitution pattern of the core moiety. Stimulant NPS that are typically associated with a distinct dopaminergic vs. serotonergic profile are pyrovalerone derivatives, phenidates, and pipradrol derivatives (Baumann et al., 2013; Duart-Castells et al., 2021; Eshleman et al., 2019; Eshleman et al., 2013; Eshleman et al., 2017; Gannon et al., 2018; Kolanos et al., 2015; Luethi et al., 2018b; Marusich et al., 2014; McLaughlin et al., 2017a; Rickli et al., 2015a; Saha et al., 2015; Simmler et al., 2014b). Most benzofurans display a distinct serotonergic vs. dopaminergic selectivity, whereas some derivatives are unselective (Brandt et al., 2020; Eshleman et al., 2019; Rickli et al., 2015b). Amphetamines and cathinones comprise both dopaminergic and serotonergic compounds. Amphetamines and cathinone derivatives that lack phenyl ring substitution generally exert distinct dopaminergic effects (Blough et al., 2019; Bonano et al., 2015; Duart-Castells et al., 2021; Eshleman et al., 2019; Eshleman et al., 2013; Eshleman et al., 2017; Maier et al., 2021; Niello et al., 2019; Rickli et al., 2015a; Simmler et al., 2013; Walther et al., 2019). Various phenyl ring substitution patterns such as para-substitution or 3,4-methylenedioxy groups shift the selectivity from DAT to SERT (Battisti et al., 2018; Baumann et al., 2012; Blough et al., 2019; Bonano et al., 2015; Eshleman et al., 2019; Eshleman et al., 2013; Eshleman et al., 2017; Luethi et al., 2018c; Luethi et al., 2019a; Mayer et al., 2019; Mayer et al., 2016; McLaughlin et al., 2017b; Niello et al., 2019; Rickli et al., 2015a; Saha et al., 2015; Simmler et al., 2014a; Solis Jr. et al., 2017; Walther et al., 2019). This also applies for NPS of other classes, such as aminoindanes, phenmetrazine derivatives, or aminorex derivatives (Eshleman et al., 2017; Halberstadt et al., 2019; Luethi et al., 2018a; Luethi et al., 2018c; Maier et al., 2018; McLaughlin et al., 2018; Rickli et al., 2019; Simmler et al., 2014b).

3.1.2. Neurochemical alterations induced by stimulant NPS

Stimulant-induced acute and chronic neurochemical alterations in rodents have been reported for various, mainly cathinone-type NPS.

Substrate-type methcathinones (0.1–10 mg/kg i.v.) and benzofurans (0.3 and 1.0 mg/kg i.v.) have been shown to elevate dopamine and 5-HT levels in rat nucleus accumbens (Brandt et al., 2020; Schindler et al., 2016; Suyama et al., 2016). *N*, α -diethylphenylethylamine, a stimulant NPS with structural similarity to methamphetamine, acutely increased dopamine and 5-HT levels in rat striatum and frontal cortex after doses of 5 and 10 mg/kg i.p. (Seol et al., 2015). Mephedrone (4-methylmethcathinone, 30 mg/kg i.p.) increased striatal dopamine, while decreasing striatal and hippocampal 5-HT in rats treated for multiple days (Motbey et al., 2012). However, even after repeated high doses of mephedrone (30 mg/kg i.p.), dopamine and 5-HT levels reversed to normal after drug cessation (Motbey et al., 2012). Schindler and colleagues reported acutely increased levels of dopamine in rat nucleus accumbens after administration of the NET/DAT inhibitors α -pyrrolidinopentiophenone (α -PVP) (0.1 and 0.3 mg/kg i.v.) and 3,4-methylenedioxypropylpyrovalerone (MDPV) (0.1 and 0.3 mg/kg i.v.) (Schindler et al., 2016; Schindler et al., 2020). In contrast, Kohler and co-workers did not detect alterations of the total monoamine content in monoamine systems related to reward after repeated administration of 1.0 mg/kg i.p. MDPV in rats (Kohler et al., 2018). Similarly, Marusich and colleagues reported only minimal changes in dopamine levels in rat brain one day after self-administration of the substrate-type cathinone mephedrone and the NET/DAT inhibitor α -PVP in form of 0.1 mg/kg infusions (Marusich et al., 2019a; Marusich et al., 2019b). These findings suggest that the dopaminergic effects of synthetic cathinones are short-lived. However, Marusich and colleagues reported altered norepinephrine, 5-HT, and glutamate levels in several rat brain regions (Marusich et al., 2019a; Marusich et al., 2019b). Repeated low-dose injections of 5 mg/kg mephedrone during adolescence period have been reported to affect monoaminergic and glutamatergic neurotransmission in rats (Kamińska et al., 2018). Additionally, injection of 5 mg/kg mephedrone induced long-lasting changes in dopamine, 5-HT, and glutamate release in the frontal cortex and nucleus accumbens, which became apparent in adulthood (Kamińska et al., 2018). In mice, cathinone NPS (3–30 mg/kg) have been shown to acutely increase striatal dopamine and 5-HT (Wojcieszak et al., 2018, 2019) and to increase prefrontal dopamine and norepinephrine (Mégarbane et al., 2020). Striatal dopamine was

however decreased when measured in the days following cathinone treatment (cumulative dose of 10–320 mg/kg i.p.) (Anneken et al., 2017; Ray et al., 2019). Similarly, striatal and prefrontal norepinephrine levels and striatal 5-HT levels have been reported to be reduced in the days following cathinone exposure (80 mg/kg i.p.) (Ray et al., 2019).

3.2. Neurological sequelae of stimulant NPS use

Various acute neurological adverse effects have been reported as a consequence of stimulant NPS use, often in combination with sympathomimetic toxicity. However, patients often present with polydrug intoxications, which typically prevents the attribution of the observed toxicity to a specific NPS (Luethi and Liechi, 2020). The para-fluorinated amphetamine analog 4-fluoroamphetamine (4-FA) has been linked to severe headache, reduced level of consciousness, coma, convulsions, and cerebral hemorrhage (Hondebrink et al., 2018). All of these symptoms were observed in polydrug users as well as in users that did not combine 4-FA with other substances. The observed toxicities may be explained by a combination of oxidative stress resulting from drug metabolism and increased catecholamine levels that may provoke vasoconstriction and microvascular dysfunction (Hondebrink et al., 2018). In vitro, 4-FA predominantly interacts with NET and DAT, which supports this hypothesis (Luethi et al., 2019a). Similarly, synthetic cathinones have been associated with headache, tremor, seizures, cerebral edema, and stroke (Beck et al., 2015, 2016; Boulanger-Gobeil et al., 2012; Forrester, 2012; Franzén et al., 2018; James et al., 2011; Ross et al., 2012; Wood et al., 2010). The majority of the above-mentioned symptoms occurred in cases of poly-drug use, including combinations of different synthetic cathinones. Nevertheless, a comparison between mono-intoxications with synthetic cathinones and poly-intoxications revealed comparable neurological outcomes (Beck et al., 2015, 2016; Forrester, 2012). As for 4-FA, these effects can mainly be explained by the potent activation of catecholaminergic systems by cathinones. Furthermore, seizures and hyponatremia caused by intoxication with cathinones have been linked to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Boulanger-Gobeil et al., 2012). Benzofuran and indole NPS have sporadically been linked to neurological adverse effects as well, which is not unexpected given the potent interactions of these substances with monoaminergic systems. However, such reports are mainly derived from polydrug intoxication cases or user reports in internet fora (Bäckberg et al., 2014; Jebadurai et al., 2013; Katselou et al., 2015). A direct attribution of these effects to benzofuran or indole NPS is therefore not possible. Neurological adverse effects of piperazine NPS include insomnia, dizziness, headache, and tremor (Gee et al., 2008; Gee et al., 2005; Wilkins et al., 2008). Furthermore, seizures are a well-documented adverse effect directly linked to piperazine use (Gee et al., 2008; Gee et al., 2010; Gee et al., 2005; Wilkins et al., 2008). The risk for seizures was reported to be associated with higher piperazine plasma levels and to be reduced by concomitant ingestion of ethanol. The high incidence of reported seizures may be linked to acute hyponatremia mediated by the serotonergic piperazines (Gee et al., 2005). MDMA and other serotonergic substances have been linked to hyponatremia, which was caused by the stimulation of arginine vasopressin release and polydipsia resulting from the effect of these substances on the serotonergic nervous pathway (Campbell and Rosner, 2008; Fallon et al., 2002; Farah and Farah, 2008; Forsling et al., 2001; Ghatol and Kazory, 2012; Hartung et al., 2002; Liu et al., 1996; Moritz et al., 2013; Rosenson et al., 2007; Simmler et al., 2011; Van Dijken et al., 2013).

In addition to the physical adverse effects associated with stimulant NPS, a variety of cognitive impairments have been reported that can be attributed to the stimulation of monoaminergic systems. The symptoms are similar for all classes of stimulant NPS and include agitation, anxiety, paranoia, panic attacks, depression, confusion, hallucinations, and delirium (Bäckberg et al., 2014; Bäckberg et al., 2016; Beck et al., 2015, 2016; Forrester, 2012; Franzén et al., 2018; Gee et al., 2010; Gee et al.,

Table 2

Overview over serotonin toxicity symptoms.

| Altered mental status | Autonomic hyperactivity | Neuromuscular hyperactivity |
|-----------------------|-------------------------|-----------------------------|
| Confusion | Hyperthermia | Akathisia |
| Agitation | Hypertonicity | Tremor |
| Excitement | Tachycardia | Myoclonus |
| Restlessness | Tachypnea | Hyperreflexia |
| Anxiety | Mydriasis | Pyramidal rigidity |
| Delirium | Diaphoresis | |
| | Hypertension | |
| | Fever | |

2005; Hondebrink et al., 2018; James et al., 2011; Jebadurai et al., 2013; Katselou et al., 2015; Penders et al., 2012; Ross et al., 2012; Wilkins et al., 2008; Wood et al., 2008; Wood et al., 2010).

3.3. Molecular mechanisms of stimulant neurotoxicity

3.3.1. Serotonin toxicity

Excessive intrasynaptic 5-HT originates from increased presynaptic release, reuptake inhibition, or monoamine oxidase (MAO) inhibition (Gillman, 2006). Furthermore, serotonergic overstimulation in the brain may be the result of 5-HT receptor agonism or antagonism (Scotton et al., 2019). Both mechanisms potentially result in serotonin toxicity, often referred to as serotonin syndrome (Isbister and Buckley, 2005). Moderate and severe serotonin toxicity has been described in intoxications with selective serotonin reuptake inhibitors (SSRIs) (Isbister et al., 2004), serotonin-norepinephrine reuptake inhibitors (SNRIs) (Foong et al., 2018), and monoamine oxidase inhibitors (MAOIs), especially when combined with other serotonergic drugs (Boyer and Shannon, 2005; Gillman, 2006; Rickli et al., 2018; Scotton et al., 2019). Accordingly, NPS that induce 5-HT release or act as agonists at 5-HT receptors may lead to serotonin toxicity. Typical symptoms of serotonin toxicity are potentially life-threatening hyperthermia and severe hypertonicity as well as fever, confusion, agitation, myoclonus, hyperreflexia, tremor, diaphoresis, and anxiety (Boyer and Shannon, 2005; Dunkley et al., 2003; Gillman, 2006; Isbister and Buckley, 2005; Scotton et al., 2019). An overview over serotonin toxicity symptoms and signs is shown in Table 2.

The serotonin 5-HT_{1A} and 5-HT_{2A} receptors have been particularly implicated in the development of serotonin toxicity. However, it is unlikely that a single receptor or selective receptor activation is solely responsible for the observed toxicity (Scotton et al., 2019). The 5-HT_{1A} and 5-HT_{2A} receptors modulate the activity of each other, whereby 5-HT_{2A} receptor activation potentiates 5-HT_{1A} receptor-induced behavior (Arnt and Hyttel, 1989). In contrast, 5-HT_{1A} receptor activation inhibits 5-HT_{2A} receptor mediated behavior such as the head twitch response (Darmani et al., 1990). It has been discussed that more severe and life-threatening symptoms of serotonin toxicity, such as hypertonicity and hyperthermia, are predominantly mediated by 5-HT_{2A} receptor activation at high 5-HT concentrations (Isbister and Buckley, 2005). This assumption is supported by evidence from in vivo studies and increased affinity of 5-HT to the 5-HT_{1A} receptor compared to the 5-HT_{2A} receptor (Eshleman et al., 2018). Hence, the 5-HT_{1A} receptor is likely to be prevalently occupied at lower extracellular 5-HT concentrations compared to the 5-HT_{2A} receptor. Therefore, it is possible that the 5-HT_{1A} receptor contributes to the early symptoms of serotonin toxicity, such as akathisia and tremor (Boyer and Shannon, 2005). The affinity of NPS at different 5-HT receptor subtypes and transporter selectivity therefore allows estimations of the risk for serotonin toxicity and its severity. The combination of stimulant NPS with other serotonergic agents, such as SSRIs, increases the risk of serotonin toxicity. This is exemplified by the case of a 22-year-old male who developed serotonin toxicity after combined intake of mephedrone and the SSRI fluoxetine (Garrett and Sweeney, 2010). Nevertheless, it needs to be considered that serotonin toxicity or similar clinical syndromes cannot be ruled out

even when the pharmacological profile suggests a substance to be distinctively dopaminergic. For instance, a 2-year retrospective analysis surprisingly revealed that one third of patients with isolated overdoses of the prescription cathinone bupropion developed serotonin toxicity (Sidlak et al., 2020). By definition, serotonin toxicity requires the administration of a serotonergic agent; however, bupropion displays a distinct dopaminergic vs. serotonergic selectivity in vitro (Shalabi et al., 2017). This suggests that dopaminergic designer cathinones may potentially induce symptoms resembling serotonin toxicity. For instance, insufflation of the dopaminergic cathinone MDPV has been reported to have induced severe serotonin toxicity in a 41-year-old female (Mugele et al., 2012). However, potential additional NPS that have remained undetected and the fentanyl treatment during her hospitalization may possibly have augmented or rather caused the serotonin toxicity (Liu et al., 1996; Mugele et al., 2012; Rickli et al., 2018). Importantly, serotonin toxicity can consequently lead to a variety of non-neurological clinical sequelae, such as SIADH (Boulanger-Gobeil et al., 2012). SIADH is a well-known adverse drug reaction of SSRIs, SNRIs (Liu et al., 1996; Oliver et al., 2020), and MDMA (Hartung et al., 2002; Liu et al., 1996; Rosenson et al., 2007; Simmler et al., 2011). Hence, increased 5-HT levels leading to antidiuretic hormone (ADH) secretion following synthetic cathinone intake may induce hyponatremia and associated complications (Simmler et al., 2011). Furthermore, rhabdomyolysis may occur as a result of hyperthermia or increased motor activity due to excessive 5-HT levels (Boulanger-Gobeil et al., 2012; Liechti, 2014; Liu et al., 1996).

Stimulant NPS toxicity to serotonergic systems has been reported in vitro as well as in vivo. Methylenedioxymethylamphetamine (MDMA) has been shown to increase the in vitro toxicity of other monoaminergic substances, such as methamphetamine and MDMA, through interaction with SERT, whereas almost no toxicity was observed for treatment with methylenedioxymethylamphetamine alone (Sogawa et al., 2011). In this study, toxicity was assessed by lactate dehydrogenase (LDH) release in Chinese hamster ovary (CHO) cells expressing monoamine and γ -aminobutyric acid (GABA) transporters and signs of toxicity started to show at a drug concentration of 100 μ M (Sogawa et al., 2011). In cultured cortical rat brain neurons, mephedrone induced a concentration-dependent cytotoxic effect (50% lethal concentration >100 μ M) (Martínez-Clemente et al., 2014). Mephedrone has furthermore been shown to induce a reduction of SERT density in rat brain (40% reduction in the frontal cortex and hippocampus and 48% reduction in the striatum after 3×25 mg/kg s.c., administered in 2 h intervals for 2 days) but it did not induce microgliosis (López-Arnau et al., 2015). Similarly, Motbey and colleagues did not detect any overt injury or lasting alteration in the serotonergic system nor any signs of neuroinflammation after ten days of chronic application of 30 mg/kg i.p. mephedrone in rats (Motbey et al., 2012). Another study in rats did however report a loss of hippocampal serotonergic neuronal markers after repeated mephedrone doses of 25 mg/kg for two days in an elevated ambient temperature, which may indicate nerve ending injuries (Martínez-Clemente et al., 2014). The stimulant 4-chloroamphetamine is a research chemical and NPS for which serotonergic neurotoxicity is relatively well described. Studies suggest the neurotoxicity of 4-chloroamphetamine to be 5-HT_{2A} receptor-independent and likely to be attributed to oxidative metabolism of 4-chloroamphetamine to reactive metabolites (Colado et al., 1993; Colado et al., 1997; Fuller, 1992; Johnson et al., 1990; Miller et al., 1986; Sprague et al., 1996). 4-Chloroamphetamine has been detected in urine samples of recreational drug users (Lin et al., 2011) but unlike other amphetamine derivatives, it never reached a high popularity as an NPS. Various aminoindane NPS were originally introduced as entactogens with reduced neurotoxic potential compared to other serotonergic entactogens such as MDMA (Johnson and Nichols, 1991; Nichols et al., 1991). However, the reputation of aminoindanes displaying reduced toxicity has since been put into question due to fatal toxicity in animal studies (Pálenčíek et al., 2016; Pinterova et al., 2017).

3.3.2. Dopamine toxicity

Several in vitro and in vivo studies showed that dopamine is neurotoxic mainly due to its high oxidizability (Graham et al., 1978; Hastings et al., 1996; McLaughlin et al., 1998; Rabinovic et al., 2000). After enzymatic or non-enzymatic oxidation, dopamine may induce oxidative stress in dopaminergic neurons and surrounding cells (Cadet and Brannock, 1998). This mechanism potentially contributes to the toxicity of dopaminergic NPS. The brain is highly sensitive to oxidative stress due to its high concentration of polyunsaturated fatty acids, the high oxygen consumption, and the presence of transition metals (Cunha-Oliveira et al., 2008). The dopamine concentration in the synaptic cleft is regulated by release, reuptake, and inactivation mechanisms. If not appropriately sequestered into vesicles, cytosolic dopamine can even after reuptake produce toxic intermediates, quinones, and reactive oxygen species (ROS) by autoxidation, metabolism, and enzymatic reactions (Carvalho et al., 2012; Goldstein et al., 2012; Graham et al., 1978; Larsen et al., 2002; Masoud et al., 2015; Stokes et al., 1999). Quinones are highly redox-active molecules that may be further oxidized to cyclic aminochromes and, if not polymerized to form melanin, are toxic to nerve endings (Bindoli et al., 1992). Conjugated to glutathione, quinones may form a glutathionyl adduct that can react with more glutathione and protein thiols resulting in glutathione depletion and formation of protein adducts (Carvalho et al., 2004). Furthermore, quinones may undergo a redox cycle forming semiquinone radicals, which lead to the generation of superoxide radicals and hydrogen peroxide (Bolton et al., 2000). Both superoxide radicals and hydrogen peroxide potentially react with transition metal ions such as iron via the Haber-Weiss/Fenton reaction, forming highly reactive hydroxyl radicals (Cadet and Brannock, 1998; Winterbourn, 1995). Hydroxyl radicals lead to oxidative stress and mitochondrial dysfunction as well as peroxidative damage at pre-synaptic membranes (Song et al., 2010). Additionally, superoxide anions may react with nitric oxide, producing the neurotoxin peroxynitrite, which can damage cellular DNA and proteins through its interaction with thiol groups (Cadet and Brannock, 1998). Notably, quinones may covalently modify and subsequently inactivate the enzyme tyrosine hydroxylase and DAT, thereby inhibiting dopamine synthesis and reuptake (Carvalho et al., 2012).

Oxidative stress also affects the ubiquitin-proteasome system, a highly regulated mechanism for intracellular protein turnover and degradation, which becomes aberrantly activated. Under normal conditions, proteins are marked for proteasomal degradation by being attached to the co-factor ubiquitin through concerted actions of a series of enzymes (Ciechanover and Brundin, 2003). During oxidative stress, the ubiquitin-proteasome system shows disturbed proteolytic cleavage and altered gene splicing. Hence, damaged proteins cannot be degraded properly anymore, leading to their accumulation in the cell and subsequently to neuronal dysfunction and potential cell death (Iacovelli et al., 2006). Therefore, if the antioxidant defense systems are not able to cope with increased ROS, substances influencing dopamine levels, such as stimulant NPS, may lead to apoptosis in dopaminergic and neighboring cells due to oxidative stress (Cadet and Brannock, 1998; Jones et al., 2000). The antioxidative defense system of the brain comprises of the enzymatic and non-enzymatic antioxidant system (Lee et al., 2020). The antioxidant enzymes include superoxide dismutase 1 and 2, peroxiredoxins, glutathione peroxidase, catalase, and glutathione reductases (Halliwell, 2006). The non-enzymatic antioxidants in the brain consist predominantly of glutathione, melatonin, and ascorbic acid (Salim, 2017). However, the brain has a comparatively weak endogenous antioxidant capacity compared to other tissues. Particularly, neurons have a very low catalase content and constrained glutathione peroxidase 4 activity, due to the low glutathione content (Lee et al., 2020).

In vitro studies in human neuroblastoma SH-SY5Y cells differentiated to a dopaminergic neuronal phenotype showed that the cathinones butylone, pentylone, and MDPV exert dose-dependent neurotoxicity starting at low millimolar concentrations (Leong et al., 2020). This neurotoxicity is characterized by a significant production of ROS,

decreased mitochondrial bioenergetics, and increased intracellular Ca^{2+} concentrations (Leong et al., 2020). Similarly, *N*-ethylhexedrone and buphedrone reduced the viability of differentiated SH-SY5Y cells at a concentration of 100 μM but only *N*-ethylhexedrone was toxic in microglia (de Mello-Sampayo et al., 2021). Wojcieszak and colleagues reported a significant decrease in cell viability of undifferentiated SH-SY5Y cells exposed to 50 μM 3-chloromethcathinone (3-CMC) and 100 μM 4-CMC for 72 h (Wojcieszak et al., 2020). The toxicity intensified after prolonged incubation, suggesting an indirect mechanism of action (Wojcieszak et al., 2020). In contrast to amphetamines, cathinones have been shown to spontaneously produce potentially toxic ROS in aqueous solution (den Hollander et al., 2015). Hence, cathinones are less toxic in differentiated SH-SY5Y cells due to their increased antioxidant capacity compared to undifferentiated cells (den Hollander et al., 2015). Furthermore, mephedrone degrades spontaneously into its toxic methylbenzamide breakdown product in aqueous solution, which contributes to the observed mephedrone toxicity (den Hollander et al., 2015). Autophagy has been shown to be involved in methylone and MDPV neurotoxicity in differentiated dopaminergic SH-SY5Y cells by increasing cellular ROS and reactive nitrogen species (RNS) levels at drug concentrations in the low millimolar range (Valente et al., 2017a). Additionally, it has been shown that methylone modulates the toxicity of other monoaminergic substances, such as methamphetamine and MDMA, through interaction with DAT (Sogawa et al., 2011). Piperazines have been shown to elicit concentration-dependent cytotoxicity and significant depletion of intracellular total glutathione in differentiated SH-SY5Y cells in the absence of genotoxicity (Arbo et al., 2016). For some piperazine NPS, signs of toxicity were already detected at low micromolar concentrations (Arbo et al., 2016). A study investigating the correlation between structure and cathinone toxicity revealed increased cytotoxicity with increasing chain length of the acyl moiety and with introduction of methyl substituents on the aryl moiety (Gaspar et al., 2018). Accordingly, highly lipophilic synthetic derivatives of the cathinone α -pyrrolidinononaphenone (α -PNP) that possess a long hydrocarbon chain have been shown to elicit toxicity in the neuronal cell line SK-N-SH at low micromolar concentrations (Morikawa et al., 2021).

In addition to neurotoxic investigations *in vitro*, dopamine toxicity induced by synthetic cathinones has been studied in rodents. Anneken and colleagues reported that 40 mg/kg mephedrone and 30 mg/kg MDPV applied four times in a binge-like regimen are not toxic to dopaminergic nerve endings in mice. Moreover, DAT blockers, such as MDPV, are protective against methamphetamine neurotoxicity, while substrate-type stimulants, such as mephedrone and methylone, accentuate methamphetamine toxicity (Anneken et al., 2015). With the intention to provide more information regarding structural elements critical for neurotoxicity, Anneken and colleagues later reported that methcathinone, the β -keto analogue of methamphetamine, significantly increased markers for dopamine nerve ending damage, starting from 10 mg/kg doses applied four times in a binge-like regimen (Anneken et al., 2017). In contrast, up to 40 mg/kg 4-methylmethamphetamine applied four times in a binge-like regimen elicited only minimal dopaminergic toxicity (Anneken et al., 2017). These results suggest that the β -keto group does not play a major role in dopamine toxicity, while para-substitution decreases it (Anneken et al., 2015; Anneken et al., 2017). It can be speculated that these observations are, at least in part, explained by decreased dopaminergic selectivity associated with para-substitution of stimulants (Luethi et al., 2019a; Niello et al., 2019; Rickli et al., 2015a). Nevertheless, high-dose mephedrone (30 mg/kg) impaired the recognition memory in rats more than a month after cessation of the drug, suggesting that mephedrone may induce major neuroadaptations (Motbey et al., 2012). Furthermore, three daily doses of 25 mg/kg *s.c.* mephedrone for two days in an elevated ambient temperature induced the loss of frontal cortex dopaminergic neuronal markers, suggesting injuries to nerve endings (Martínez-Clemente et al., 2014). It has further been shown that the same dose regimen of mephedrone induces a reduction of the densities of DAT (30% in the frontal

cortex) accompanied by a parallel decrease in the expression of tyrosine hydroxylase and tryptophan hydroxylase 2 (López-Arnau et al., 2015). These findings suggest a down-regulation of dopamine D_2 receptors in the striatum. Additionally, mephedrone induced oxidative stress in the frontal cortex accompanied by increased glutathione peroxidase levels in the brain (López-Arnau et al., 2015). Oxidative stress may also be induced or accentuated by hyperthermia, which can be elicited by psychoactive stimulants (Callaway and Clark, 1994; Liechti, 2014). Increased body temperature has been reported after MDPV and butylone ingestion in humans (Borek and Holstege, 2012; Zaami et al., 2018). Similarly, 5 mg/kg *s.c.* cathinone, alone or in combination with caffeine, as well as 10 mg/kg *i.p.* methcathinone have been reported to increase the body temperature in rodents (Alsufyani and Docherty, 2017; Shortall et al., 2013). In contrast, 10 mg/kg *i.p.* mephedrone reduced the rectal temperature in rodents, which was enhanced by α_1 -adrenoceptor and dopamine D_1 receptor blockade (Shortall et al., 2013). Hence, studies in rodents do not always reflect the temperature actions in humans but are useful to investigate the influence of additional factors including ambient temperature, sex, or stressors on the effect and toxicity of stimulants (Docherty and Green, 2010).

3.3.3. ROS production by oxidative deamination

Substrate-type stimulant NPS can be expected to produce ROS and oxidative stress based on their potential to release monoamines from neuronal storage vesicles. If not stored in vesicles, cytoplasmic norepinephrine, dopamine, and 5-HT will partly be metabolized by MAO, a flavoenzyme which is localized at the outer mitochondrial membrane (Schnaitman et al., 1967). As aforementioned, oxidative deamination produces hydrogen peroxide as side product, which forms the highly reactive hydroxyl radicals in the presence of transition metal ions. In mouse brain synaptosomes incubated with dopamine or 5-HT, hydrogen peroxide generation is MAO-dependent (Barbosa et al., 2012). Two isoforms of MAO have been described in the CNS; MAO-A is predominantly expressed in catecholaminergic neurons and MAO-B is expressed in serotonergic neurons, astrocytes, and glia (Shih et al., 2000). Hence, MAO-B metabolizes 5-HT in serotonergic neurons even though *in vitro* MAO-A displays higher affinity for norepinephrine and 5-HT compared to MAO-B (Alves et al., 2009; Alves et al., 2007; Johnston, 1968). Dopamine and tyramine are equipotently metabolized by MAO-A and MAO-B (Shih et al., 2000). Oxidative deamination of dopamine by MAO produces the toxic aldehyde intermediate 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is further oxidized to 3,4-dihydroxyphenylacetic acid (DOPAC) via aldehyde dehydrogenase (ALDH) (Jinsmaa et al., 2009). This reaction is accompanied by the reduction of oxygen to hydrogen peroxide (Hauptmann et al., 1996).

3.3.4. Mitochondrial toxicity

The maintenance of the mitochondrial function is crucial for cell survival. Especially the neuronal homeostasis depends on the integrity of mitochondria. Hence, to ensure unimpeded mitochondrial function, various mitochondrial defense mechanisms have evolved. Such mechanisms include ROS scavenging, degradation of faulty mitochondrial proteins, and turnover of organelles (Karbowski and Neutzner, 2012). Excessive ROS production following stimulant use can lead to oxidative damage of the mitochondria, initiating an intracellular cascade resulting in neurotoxicity (Carvalho et al., 2012). The enzyme complexes I and III of the mitochondrial respiratory chain represent potential sites for ROS generation (Dröse and Brandt, 2012). Disruption of the mitochondrial respiratory chain by stimulant NPS can result in decreased glutathione levels in neuronal cells (Valente et al., 2017b). Mitochondrial impairment furthermore results in mitochondrial membrane potential ($\Delta\psi\text{m}$) dissipation and depletion of cellular ATP stores (Luethi et al., 2017; Valente et al., 2017b). Subsequently, ROS accumulation can lead to opening of the mitochondrial permeability transition pore (mPTP) and release of cytochrome *c* into the cytoplasm, followed by caspase activation and apoptosis (Eguchi et al., 1997; Green and Reed, 1998).

When administered at low millimolar concentrations, the synthetic cathinones mephedrone, methylone, and MDPV have been shown to impair the mitochondrial respiration in differentiated SH-SY5Y cells with subsequent increase in ROS and partly also RNS (den Hollander et al., 2015; Leong et al., 2020; Valente et al., 2017b). Furthermore, several cathinone NPS at millimolar concentrations have been identified as mitochondrial toxicants as they impaired the mitochondrial electron transport chain, which led to depletion of the cellular ATP stores (Luethi et al., 2017; Luethi et al., 2019a; Valente et al., 2017b). In differentiated SH-SY5Y cells, para-halogenation of methcathinones increased their neurotoxic properties, which has been attributed to the impairment of mitochondrial function and subsequent induction of apoptosis (Zhou et al., 2020b). Most signs of toxicity were observed at millimolar concentrations only. However, 4-CMC significantly decreased the basal oxygen consumption in differentiated SH-SY5Y cells already at 200 μM (Zhou et al., 2020b). Hyperthermic conditions have been shown to further increase the mitochondrial superoxide production and to decrease the oxygen consumption rate following methcathinone derivatives exposure in differentiated SH-SY5Y cells (Zhou et al., 2020a). Despite the stimulation of protective mechanisms, such as the 70 kilodalton heat shock protein (Hsp70), autophagy and a shift from apoptosis to necrosis was induced (Zhou et al., 2020a). Moreover, apoptosis with evident chromatin condensation and formation of pyknotic nuclei as well as increased intracellular Ca^{2+} concentrations and activation of caspases 3, 8, and 9 has been observed for various synthetic cathinones at millimolar concentrations (Leong et al., 2020; Valente et al., 2017b). Similarly, apoptosis induced by α -PNP derivatives in neuronal SK-N-SH cells was preceded by ROS and RNS production, mitochondrial dysfunction, cytochrome c release, and activation of caspases 3 and 9 (Morikawa et al., 2021). These signs of toxicity already became evident at low micromolar doses (Morikawa et al., 2021). A study in mitochondria from rat hippocampus, cortex, and cerebellum showed that low micromolar concentrations of mephedrone increased ROS levels, impaired the mitochondrial membrane potential, induced mitochondrial swelling, and damaged the mitochondrial outer membrane, which was associated with cytochrome c release in all investigated brain regions (Naserzadeh et al., 2019). Additionally, oxidative phosphorylation was impaired by mephedrone, resulting in decreased ATP levels (Naserzadeh et al., 2019). The piperazine derivatives benzylpiperazine (BZP) and benzoylpiperazine were shown to be cytotoxic in differentiated SH-SY5Y cells by impairing the activity of the mitochondrial complex I at high concentrations (500 μM), which leads to ROS production and lipid peroxidation (Katz et al., 2018). Furthermore, piperazines at concentrations of 50–2000 μM have been shown to elicit cytotoxicity in differentiated SH-SY5Y cells, accompanied by mitochondrial hyperpolarization, leading to early apoptosis (Arbo et al., 2016). Similarly, piperazines induced cytotoxicity at similar concentrations through mitochondrial impairment and activation of mitochondrial proapoptotic pathways in non-neuronal cell lines (Arbo et al., 2014; Persona et al., 2016).

4. Psychedelic NPS

Serotonergic psychedelics have a rich history of religious use and have since found their way into psychotherapy and onto the black market. Psychedelics interact with various pharmacological targets but altered perception and cognitive states are mainly attributed to agonism at 5-HT_{2A} receptors (Geyer and Vollenweider, 2008; Holze et al., 2021; Kraehenmann et al., 2017; Madsen et al., 2019; Nichols, 2004, 2016; Preller et al., 2018; Vollenweider et al., 1998). Substituted phenethylamines, tryptamines, and lysergamides make up the main groups of psychedelic NPS. Phenethylamine NPS are derivatives of mescaline (3,4,5-trimethoxyphenethylamine), tryptamine NPS display similarity to the traditional tryptamines *N,N*-dimethyltryptamine (DMT) and psilocybin, and lysergamide NPS are variations of the ergot alkaloid lysergic acid diethylamide (LSD). Classic psychedelics including

mescaline, psilocybin, and LSD are considered to be not neurotoxic besides from their acute transient alteration of the mind (Liechti, 2017; Liu et al., 1996; Nichols, 2016; Nichols and Grob, 2018). However, only very little information is available regarding the neurotoxic potential of psychedelic NPS.

4.1. Pharmacology of psychedelic NPS

4.1.1. Monoamine receptor and transporter interaction profiles of psychedelic NPS

In addition to partial to full agonism at 5-HT_{2A} receptors, psychedelic NPS activate other serotonergic receptors, such as the 5-HT_{2B} and 5-HT_{2C} receptor subtypes (Eshleman et al., 2018; Jensen et al., 2017; Kolaczynska et al., 2019; Luethi and Liechti, 2020; Luethi et al., 2018d; Luethi et al., 2019b; Moya et al., 2007; Rickli et al., 2015c; Rickli et al., 2016). Furthermore, psychedelic NPS have been shown to interact with other targets, including adrenergic, dopaminergic, and histaminergic receptors, μ -opioid receptors, cannabinoid receptor type 1, monoamine transporters, and MAOs (Åstrand et al., 2020; Eshleman et al., 2018; Kolaczynska et al., 2019; Luethi and Liechti, 2020; Luethi et al., 2018d; Luethi et al., 2019b; Noble et al., 2018; Rickli et al., 2015c; Rickli et al., 2016; Wagmann et al., 2019). However, compared to the potent agonism at serotonergic receptors, interactions with other monoaminergic receptors are mostly weak. Various NBOME derivatives inhibit NET and SERT at low micromolar concentrations (Eshleman et al., 2018; Rickli et al., 2015c). Similarly, various tryptamine NPS inhibit norepinephrine and 5-HT uptake with some derivatives displaying substrate activity at SERT (Rickli et al., 2016). LSD does not show relevant interactions with monoamine transporters, suggesting that this applies for lysergamide NPS as well (Eshleman et al., 2018; Rickli et al., 2015c).

4.1.2. Neurochemical alterations induced by psychedelic NPS

For a few psychedelic NPS, substance-induced neurochemical alterations have been assessed in vivo. Phenethylamine NPS have been demonstrated to increase extracellular acetylcholine, glutamate, dopamine, and 5-HT levels in rodent striatum and nucleus accumbens (Custodio et al., 2020; Miliano et al., 2019; Páleníček et al., 2013; Wojtas et al., 2021). NBOME derivatives have furthermore been shown to increase acetylcholine, glutamate, dopamine, and 5-HT release in rat frontal cortex (Herian et al., 2020; Wojtas et al., 2021). In rats treated with 25I-NBOME (1 and 3 mg/kg), inhibition of serotonin 5-HT_{2A} and 5-HT_{2C} receptors abolished the increase in glutamate, dopamine, and 5-HT release from cortical neuronal terminals, whereas 5-HT_{1A} receptor inhibition counteracted dopamine and 5-HT release only (Herian et al., 2020). In addition, exposure to NBOME derivatives may affect the expression of several proteins involved in dopaminergic effects. Repeated administration of 1 mg/kg 25B-NBOME for seven days has been shown to increase expression of the dopaminergic D₁ receptor in murine nucleus accumbens, while decreasing the expression of the dopaminergic D₂ receptor (Custodio et al., 2020). In another study, repeated administration of 25N-NBOME decreased expression levels of the dopaminergic D₂ receptor, DAT, and tyrosine hydroxylase in murine nucleus accumbens (Seo et al., 2019). However, it did not alter the expression of the dopaminergic D₁ receptor (Seo et al., 2019). In the murine ventral tegmental area, 7-day treatment with 1 mg/kg 25B-NBOME decreased the expression of the dopaminergic D₂ receptor and DAT, while not affecting tyrosine hydroxylase expression (Custodio et al., 2020). In the dorsal striatum of mice repeatedly treated with 0.3–3 mg/kg i.p. 25N-NBOME, expression of the dopaminergic D₂ receptor was decreased, while expression of the dopaminergic D₁ receptor, DAT, and tyrosine hydroxylase were unaffected (Seo et al., 2019). Additionally, repeated administration of NBOME derivatives may affect the expression of proteins involved in neuroadaptation. For instance, 1 mg/kg 25B-NBOME for seven days was shown to increase the expression of phosphorylated cAMP-responsive element-binding protein (p-CREB) and deltaFosB (ΔFosB) but it decreased brain-derived neurotrophic factor

(BDNF) protein levels in murine nucleus accumbens (Custodio et al., 2020).

4.2. Neurological sequelae of psychedelic NPS use

Psychedelic NPS are appreciated by users for their potential to transiently alter mood, perception, and cognition. However, in predisposed individuals such altered states may potentially induce psychological disturbances. Classic serotonergic psychedelics have low physiological toxicity (Nichols, 2016; Nichols and Grob, 2018). In contrast, some novel psychedelics, including NBOMe derivatives, have been linked to a variety of adverse effects and even death (Halberstadt, 2017; Luethi and Liechti, 2020). NBOMe derivatives display an increased potency and an increased risk for seizures compared to non-NBOMe phenethylamines (Eshleman et al., 2018; Forrester, 2013, 2014; Grautoff and Kähler, 2014; Halberstadt, 2017; Heim, 2004; Hill et al., 2013; Iwersen-Bergmann et al., 2019; Rickli et al., 2015c; Srisuma et al., 2015; Stellpflug et al., 2014; Wood et al., 2015). Compared to other psychedelics, NBOMe derivatives display a significantly increased selectivity for 5-HT_{2A} vs. 5-HT_{1A} receptors, which may explain the increased risk for seizures (Eshleman et al., 2018; Gharedaghi et al., 2014; Rickli et al., 2015c). Other severe neurological adverse effects, including cerebral vasculopathy, cerebral edema, and serotonin toxicity, have been associated with phenethylamine NPS (Ambrose et al., 2010; Bosak et al., 2013; Spoelder et al., 2019). However, other substances including cannabinoids, benzodiazepines, or opioids could have contributed to the observed symptoms in these cases. Phenethylamine NPS may induce psychological adverse effects resulting from the potent interactions with serotonergic receptors. Such adverse effects include agitation, aggression, anxiety, paranoia, confusion, visual and auditory hallucinations, and psychosis (Forrester, 2013, 2014; Halberstadt, 2017; Hermanns-Clausen et al., 2017; Hill et al., 2013; Huang and Bai, 2011; Iwersen-Bergmann et al., 2019; Srisuma et al., 2015; Stellpflug et al., 2014; Stoller et al., 2017; Wood et al., 2015). Similarly, tryptamine NPS have been linked to cognitive disturbances including agitation, anxiety, confusion, disorientation, perceptual disturbances, and hallucinations (Alatrash et al., 2006; Boland et al., 2005; Ikeda et al., 2005; Itokawa et al., 2007; Meatherall and Sharma, 2003). There is currently virtually no information available regarding neurological consequences of lysergamide NPS use. However, the structural and pharmacological similarity to LSD suggests potential psychological symptoms associated with the potent psychedelic properties of lysergamides. Such symptoms include agitation, anxiety, confusion, or hallucinations (Grumann et al., 2019). A recent report of LSD-induced seizure and cerebral injury furthermore suggests that in rare cases, lysergamide NPS may potentially induce severe neurological sequelae as well (Aakerøy et al., 2020). However, psychedelics have also been shown to induce neurogenesis and their use is not generally associated with psychiatric disorders in contrast to other drugs of abuse (Krebs and Johansen, 2013; Ly et al., 2018).

4.3. Suggested mechanisms that could contribute to neurotoxicity

Different mechanisms of neurotoxicity have been described for psychedelic NPS. Using microelectrode arrays, 4-bromo-2,5-dimethoxyphenylethylamine (2C-B) and 25B-NBOMe have been shown to rapidly and concentration-dependently decrease the weighted mean firing rate (IC₅₀ of 27 and 2.4 μ M, respectively) and the weighted mean burst rate (IC₅₀ of 39 and 3.3 μ M, respectively) in rat cortical cultures (Zwartzen et al., 2018). Various 4-substituted-2,5-dimethoxyphenethylamines (2C derivatives) at concentrations of 100 μ M or higher have been described to mediate LDH release in cells derived from dopaminergic and serotonergic neurons, indicative of cell membrane integrity loss and cell death (Asanuma et al., 2020). α -Etyltryptamine (8 \times 30 mg/kg s.c.) reduced the number of 5-HT uptake sites in rat frontal cortex which was accompanied by decreased 5-HT levels one week after the last dose

(Huang et al., 1991). The tryptamine NPS 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MiPT) has been shown to induce apoptotic cell death through caspase activity in mouse brain at high doses (2.7 mg/kg) (Altunci et al., 2021). Similarly, some 2C derivatives induced apoptotic morphological changes and increased oxidative stress in B65 neuroblastoma cells at concentrations of 50 μ M and higher (Asanuma et al., 2020). 25C-NBOMe at similar concentrations was shown to elicit toxicity in SH-SY5Y, PC12, and SN4741 cells, which all express monoaminergic targets (i.e., serotonin 5-HT_{2A} receptors and/or DAT) (Xu et al., 2019). A proposed mechanism of neurotoxicity is the inhibition of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway and the activation of the mitogen-activated protein kinase kinase (MAPKK)/extracellular signal-regulated kinase (ERK) pathway (Xu et al., 2019). Both 2C and NBOMe derivatives showed higher in vitro neurotoxicity when compared to methamphetamine (Asanuma et al., 2020; Xu et al., 2019). However, it needs to be considered that compared to methamphetamine, these psychedelics are used at lower doses, resulting in lower blood levels. In mice treated with 2C derivatives at 10 mg/kg, Kim and colleagues reported altered levels of dopaminergic signaling proteins in the nucleus accumbens and the medial prefrontal cortex as well as increased c-Fos expression in the nucleus accumbens (Kim et al., 2021). Furthermore, treatment with high doses of 2C derivatives (15–60 mg/kg) induced motor function impairments and memory deficits, and enhanced microgliosis in the striatum (Kim et al., 2021).

As for stimulants, the 5-HT_{2A} receptor has been suggested to play a role in psychedelic-induced neurotoxicity (Capela et al., 2006). Cell death in cortical neuronal cultures mediated by 25–100 μ M of the psychedelic amphetamine derivative 4-iodo-2,5-dimethoxyamphetamine (DOI) could be partially prevented by 5-HT_{2A} receptor antagonists (Capela et al., 2006). In another study, DOI itself was shown to counteract developmental neurotoxicity of ethanol to serotonergic neurons (Ishiguro et al., 2016). 5-Methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT) was shown to activate apoptotic signals and to produce DNA single- and double-strand breaks in the rat cortex after an injection of 2.5–10 mg/kg s.c. (Noworyta-Sokolowska et al., 2016; Noworyta-Sokolowska et al., 2019). Similarly, 25B-NBOMe at doses up to 3 mg/kg s.c. produced minor DNA damage in the rat frontal cortex (Wojtas et al., 2021).

5. Concluding remarks

Stimulant and psychedelic NPS acutely affect monoaminergic systems and induce changes in neurochemistry. Rarely, intake of such compounds may lead to potentially severe neurological adverse effects. However, the precise evaluation of the degree of involvement of individual NPS to neurological sequelae in patients is hindered by the high proportion of polydrug intoxications.

A variety of studies documented the neurotoxic potential of stimulant and psychedelic NPS in vitro and in vivo. However, it needs to be taken into account that in most in vitro studies toxicity was only observed after long incubation times and at very high substance concentrations (i.e., high micromolar to low millimolar range). These studies are very valuable as they provide information regarding the mechanisms, which are potentially involved in NPS neurotoxicity. However, the used concentrations are mostly not representative for typical pharmacological NPS concentrations in users (Elliott and Evans, 2014; Marinetti and Antonides, 2013). Nevertheless, it needs to be considered that in heavy intoxication cases, plasma NPS levels may exceed the low micromolar range and furthermore, tissue concentrations may be substantially higher than blood concentrations (Elliott and Evans, 2014; Marinetti and Antonides, 2013). Furthermore, contributing factors, such as hyperthermia, polydrug intoxication, metabolic predisposition, and user susceptibilities, may render NPS substantially more neurotoxic than might be expected from studies in cell lines or rodents. Moreover, it has been shown that by mimicking a more realistic

approach of the in vivo situation, for instance by applying a mixture of parent compound and its metabolites at increased temperature, stimulant-induced in vitro neurotoxicity may occur at in vivo relevant concentrations (Barbosa et al., 2014).

Stimulant NPS primarily interact with monoamine transporters and therefore potentially induce neurotoxicity related to increased monoamine concentrations. Additionally, direct cellular and/or mitochondrial toxicity, increased ROS levels induced by reactive metabolites, mitochondrial dysfunction, or monoaminergic deamination possibly contribute to neurotoxicity of stimulant NPS. Serotonin 5-HT_{2A} receptor activation as well as oxidative stress and apoptotic cell death have been suggested as mechanisms that could potentially lead to psychedelic NPS-induced neurotoxicity. Unclear, however, remains the extent to which the above-mentioned mechanisms contribute to adverse effects of stimulant and psychedelic NPS in humans.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by grants from the Swiss National Science Foundation (SNSF; grant No. P2BSP3_191740 to D.R. and grant No. P400PM_191032 to D.L.) and the Federal Office of Public Health (BAG; grant No. 16.921318 to M.E.L.).

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