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REVIEW ARTICLE

The hallucinogenic world of tryptamines: an updated review

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Abstract In the area of psychotropic drugs, tryptamines are known to be a broad class of classical or serotonergic hallucinogens. These drugs are capable of producing profound changes in sensory perception, mood and thought in humans and act primarily as agonists of the 5-HT_{2A} receptor. Well-known tryptamines such as psilocybin contained in Aztec sacred mushrooms and *N*,*N*-dimethyltryptamine (DMT), present in South American psychoactive beverage ayahuasca, have been restrictedly used since ancient times in sociocultural and ritual contexts. However, with the discovery of hallucinogenic properties of lysergic acid diethylamide (LSD) in mid-1900s, tryptamines began to be used recreationally among young people. More recently, new synthetically produced tryptamine hallucinogens, such as alpha-methyltryptamine (AMT), 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) and 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), emerged in the recreational drug market, which have been claimed as the next-generation designer drugs to replace LSD ('legal' alternatives to LSD). Tryptamine derivatives are widely accessible over the Internet through companies selling them as 'research chemicals', but can also be sold in 'headshops' and street dealers. Reports of intoxication and deaths related to the use of new tryptamines have been described over the last years, raising international concern over tryptamines. However, the lack of literature pertaining to pharmacological and toxicological properties of new tryptamine hallucinogens hampers the assessment of their actual potential harm to general public health. This review provides a comprehensive update on tryptamine hallucinogens, concerning their historical background, prevalence, patterns of use and legal status, chemistry, toxicokinetics, toxicodynamics and their physiological and toxicological effects on animals and humans.

Keywords Tryptamines · Hallucinogens · 5-HT_{2A} receptor · Toxicokinetics · Toxicodynamics · Toxicity

Introduction

Recreational drugs have always played a part in human society, but, in recent years, the drug market has changed significantly. In addition to the well-known illicit drugs such as cocaine, amphetamine, heroin or lysergic acid diethylamide (LSD), many new psychoactive substances have appeared at a dizzying speed (EMCDDA 2014; Schmidt et al. 2011). The illegal status of the classical drugs of abuse has encouraged users to obtain these new options with similar pharmacological effects, having the advantages of being legal and cheaper and, theoretically, of having higher purity (Hill and Thomas 2011). These new substances are usually synthetic chemicals, but may also be products from natural sources, including plant or fungal materials that can be easily purchased on the Internet Web sites or through specialized stores (Arunotayanun and Gibbons 2012; EMCDDA 2014) and appear in a variety of forms, such as 'party pills' or herbal mixtures (Babu et al. 2005; EMCDDA 2010; Kjellgren and Soussan 2011). Although these substances

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are sold in packages labeled 'not for human consumption', they are intentionally marketed as replacements for illegal drugs, being sold legally in certain countries under names such as 'research chemicals', 'legal highs' or 'designer drugs' (Arunotayanun and Gibbons 2012; Kjellgren and Soussan 2011; Musselman and Hampton 2014). These new psychoactive substances, in fact, refer to substances typically created by the modification of the molecular structure of controlled psychoactive molecules or, less commonly, by finding new drug classes, in order to create alternative psychoactive compounds and to circumvent drug abuse legislation (Gibbons 2012; Hill and Thomas 2011).

More than 300 different new psychoactive substances have been synthesized since the beginning of the twenty-first century, and the number identified in the European Union has risen abruptly from 14 in 2005 to 81 only in 2013 (EMCDDA 2014). These substances may belong to different chemical classes such as tryptamines, phenethylamines, cathinone derivatives, synthetic cannabinoids, and piperazines (EMCDDA 2014). In 2012, four new tryptamine derivatives were formally notified to the Early Warning System (EMCDDA 2012). Although that may seem a small number, it is more than what was notified in the previous 3 years combined. In fact, among the recently highlighted new psychoactive substances, the demand for synthetic tryptamines has won popularity in the last few years (EMCDDA 2014) due to their hallucinogenic properties, replacing the consumption of the traditional hallucinogens (Winstock et al. 2014).

Scanty information is available on these new tryptamine derivatives, which are rarely subject to studies in animals or humans, so that the real composition of these products, their acute and long-term effects, their possible interactions with other substances, their toxicological risks or even their addictive potential remain unknown (Sanders et al. 2008; Schmidt et al. 2011). The escalating market of these products resulted in a consequential increase of intoxication cases and deaths related to their consumption (Boland et al. 2005; Jovel et al. 2014; Tanaka et al. 2006). While comprehensive and updated reviews are available for some new psychoactive substances such as cathinones (Katz et al. 2014; Prosser and Nelson 2012; Valente et al. 2014), piperazines (Arbo et al. 2012; Elliott 2011; Monteiro et al. 2013) and synthetic cannabinoids (Seely et al. 2012), to our knowledge this is the first paper gathering data on the chemical, pharmacological and toxicological properties of currently known tryptamine derivatives.

What is a hallucinogen? The definition

In general, hallucinogens are defined as agents that produce changes in thought, perception and mood without producing memory or intellectual impairment or addiction and that produce minimal autonomic side effects (Hollister 1964). However, this definition may be considered too restricted and is also often controversial, because besides the two main hallucinogenic classes (indolamines and phenylalkylamines; see below section: "Chemistry"), other drug classes generally not classified as hallucinogens, such as cannabinoids and *N*-methyl-D-aspartate (NMDA) antagonists, may also produce effects that overlap with those; these drugs showed to be behaviorally dissimilar in humans and have distinct mechanisms of action. Subsequently, Glennon (1996) added to the definition that the hallucinogens are also agents that have the 5-HT_{2A} receptors as primary site of action and produce full substitution in animals trained to discriminate the hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM). For this reason, these drugs are also known as classical or serotonergic hallucinogens.

The evolution in the use of tryptamines: from natural substances to synthetic drugs

Nature is an astonishing 'laboratory' that has the ability to produce compounds that cause profound effects on several organs, including the central nervous system (CNS). Since prehistory, humans have used these compounds, particularly naturally occurring hallucinogens, taking advantage of their psychotropic properties for many purposes (Metzner 1998; Nichols 2004; Sanders et al. 2008).

Ayahuasca, also known as 'vine of the souls', is a hallucinogenic brew made out of *Banisteriopsis caapi* alone or in combination with other plants, as *Psychotria viridis*. Rivier and Lindgren (1972) identified the chemicals responsible for the effects of this brew: the *Banisteriopsis caapi* is the source of the major β-carbonile alkaloids harmine, harmaline and tetrahydroharmine (THH), while the leaves of *Psychotria viridis* are rich in *N*,*N*-dimethyltryptamine (DMT). After oral administration in humans, DMT is rapidly inactivated by monoamine oxidase A (MAO-A) enzymes in the liver and gut; however, *B. caapi* contains MAO inhibitors (harmine and harmaline) that prevent the DMT degradation, and therefore, the combination of the two plants is essential for the enhancement of the effects (Cunningham 2008; McKenna 2004). Indigenous Amazonian tribes traditionally use this drink in religious ceremonies. It is also used in Northern South America with therapeutic purposes, believed to be effective in the treatment of abuse disorders and some physical maladies (McKenna 2004; Ujvary 2014). Ayahuasca is probably the most common tea with ethnomedicine applications, containing considerable amounts of DMT (an average dose of 100 mL of ayahuasca contains approximately 24 mg of DMT) (Callaway et al. 1996). DMT also occurs in other plant sources

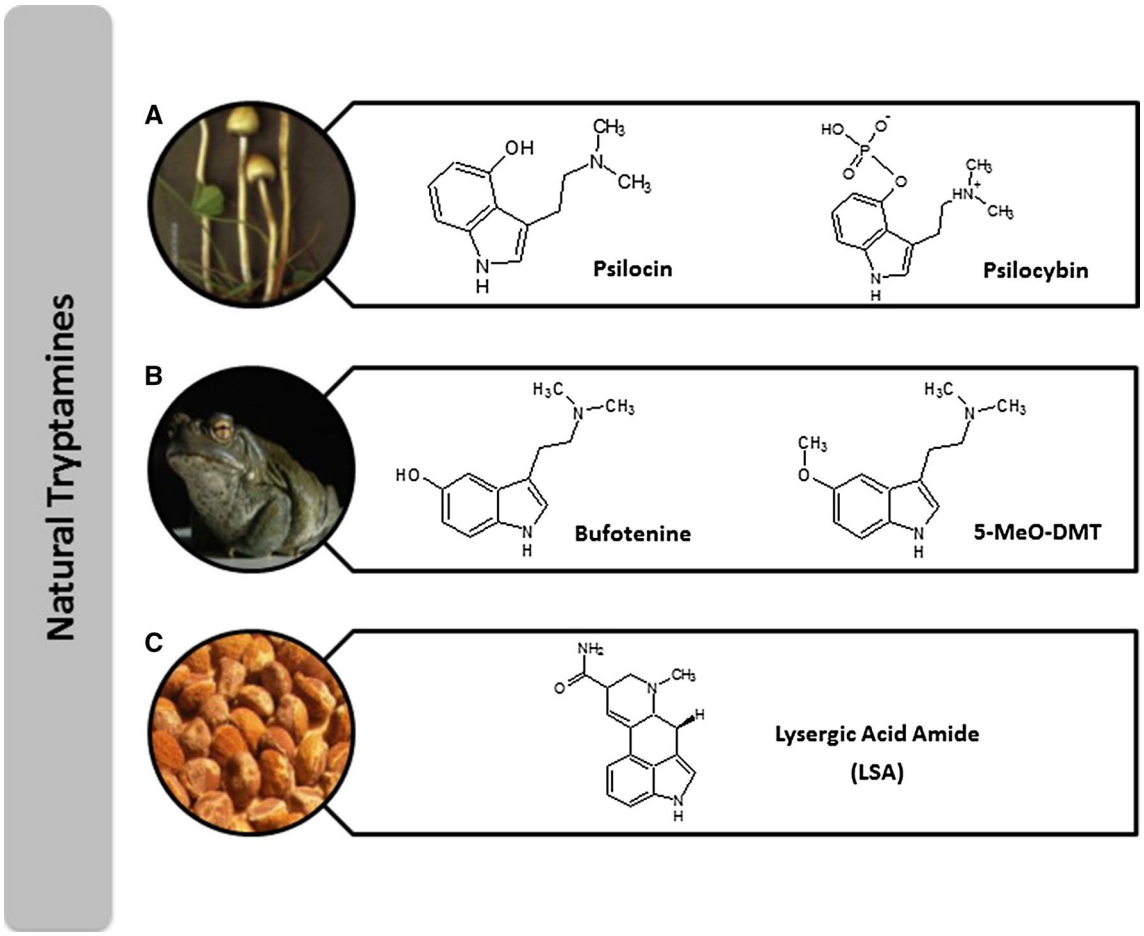


Fig. 1 Molecular structures of the best-known natural hallucinogenic tryptamines. **a** Psilocin and psilocybin are the main hallucinogenic compounds of the *Psilocybe* spp. mushrooms; **b** the desert toad *Bufo alvarius* is known to secret the psychoactive substances bufotenine and 5-MeO-DMT; **c** LSA, a natural analog of the LSD, may be found in seeds of plants such as *Argyreia nervosa*

(e.g., in the species *Desmanthus illinoensis*, *Phalaris arundinacea*, *Phalaris aquatic*, *Mimosa hostilis* or *Phalaris tuberosa*) (Halpern 2004; Shulgin and Shulgin 1997) and is also considered endogenous, having been detected in trace amounts in mammalian brains as well as in the blood and urine of healthy humans (Barker et al. 2012; Christian et al. 1977; Franzen and Gross 1965). This hallucinogenic compound was isolated from the seeds of *Piptadenia* species by Fish et al. (1955a) although Manske (1931) is credited as the first to have synthesized this substance. One year later, Szara demonstrated, for the first time, that DMT induces visual hallucinations, spatial distortions, speech disturbance and euphoria when administered intramuscularly in humans (Szara 1956). In the United Kingdom (UK), DMT is categorized as a Class A substance and in the USA it is considered as a Schedule I drug (Arunotayanun and Gibbons 2012; Winstock et al. 2014), although recent rules established by the US Supreme Court now protect the religious use of ayahuasca in the USA (Bullis 2008; Cakic et al. 2010).

The most common hallucinogenic fungi containing tryptamine derivatives are the *Psilocybe* spp. mushrooms, which are widely distributed around the world, being extremely used by indigenous people for centuries in sacred rituals, especially in South American countries (particularly in Colombia), Mexico, India, Japan, New Guinea and Australia (Matsushima et al. 2009). Studies on the chemical composition of the psychoactive mushrooms have focused on the two main hallucinogenic compounds, namely psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) and psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine) (Fig. 1), which are thermostable, not being inactivated by preparations involving temperature cycles (Schwartz and Smith 1988). These naturally occurring tryptamines were isolated for the first time in 1958 (Badham 1984; Wurst et al. 2002). Psilocybin and psilocin have LSD-like properties and produce changes in perception and behavior (Cunningham 2008). Thus, psychoactive mushrooms soon became known worldwide as 'magic mushrooms' and have turned famous among recreational users in the USA, Europe and Japan.

In the UK, the *Psilocybe semilanceata* species is the most used one for recreational purposes (Arunotayanun and Gibbons 2012). Currently, Psilocybe mushrooms, psilocybin and psilocin are classified as Schedule I drugs in the USA, although the spores of mushrooms remain legal (with the exception of California) (Halpern 2004).

Another known natural tryptamine is bufotenine or 5-hydroxy-*N*,*N*-dimethyltryptamine (5-OH-DMT), an *N*-alkylated derivative of serotonin and also a structural isomer of psilocin (Chamakura 1994). During World War I, Handovsky (1920) isolated bufotenine, while in 1934 Wieland (Wieland et al. 1934) established its chemical structure and in 1935 Hoshino (Hoshino and Shimodaira 1935) synthesized it for the first time. Bufotenine and its derivative 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) are the main psychoactive ingredients of the secretion of the American desert toad, *Bufo alvarius* (Fig. 1) (Weil and Davis 1994), and have been used in the production of hallucinogenic snuff in South America (Babu et al. 2005; Chamakura 1994; Ujvary 2014). As with other tryptamines previously described, the bufotenine appears in many hallucinogenic plants (Chamakura 1994; Moretti et al. 2006). Noteworthy, several methylated tryptamines have been detected as endogenous compounds in humans too, though their biological roles are still unclear. 5-MeO-DMT can be synthesized in human pineal gland and has been detected in both pineal gland and urine (Guchhait 1976; Narasimhachari et al. 1971). The methylated indolamines are also present in retina at relatively high levels (Leino and Airaksinen 1985). Bufotenine itself can have endogenous origin too (Barker et al. 2012) since 5-MeO-DMT is oxidatively demethylated to bufotenine in the human body (Shen et al. 2010).

The practice of using consciousness-altering substances was followed by mankind for millennia, but mostly within a therapeutic, cultural and religious context (Metzner 1998; Nichols 2004; Sanders et al. 2008). However, these substances have recently attracted the attention of Western researchers that, by altering the chemical structure of well-known millenary natural tryptamines, created new synthetic psychoactive substances, which gained prominent popularity in recreational drugs scenarios, resulting in their widespread propagation and abuse. The chemist Alexander Shulgin synthesized several hundred substituted tryptamines, of which about 50 are known to be psychoactive and currently used for recreational purposes. Their synthesis, doses and adverse effects are described in his book-'TIHKAL' (Tryptamines: I Have Known and Loved) (Shulgin and Shulgin 1997).

LSD is the best-known synthetic hallucinogenic drug. Although LSD does not occur in nature, a similar analog, lysergic acid amine (LSA), is found in seeds of *Argyreia nervosa* and *Ipomoea violacea* used in Central America for shamanic and ceremonial purposes (Halpern 2004). Synthesized by Hofmann in 1938, LSD's consciousness-altering properties were discovered accidentally a few years later (Hagenbach and Werthmuller 2011; Hofmann 1976). Its molecular structure and mechanism of action present similarities with serotonin, which prompted the evaluation of its potential therapeutic use in alcoholics and patients with mental disorders (Nichols 2013). The publicity about LSD has led to great interest and use among young people. Consequently, in 1966, LSD was banned and in 1970 was reclassified as a Schedule I controlled substance in an attempt to avoid its growing recreational use (Smith et al. 2014).

The use of hallucinogens is lower than that of stimulants or cannabinoids, but, at this time, there are on the market more hallucinogenic substances than ever before (EMCDDA 2014). Alpha-methyltryptamine (AMT), a substituted tryptamine, was developed in the Soviet Union, in the 1960s, as an antidepressant under the name of Indopan. At the same time, the Upjohn Pharmaceutical Company studied its clinical value, which proved to be reduced. Despite having no therapeutic applicability, its popularity as a 'designer drug' has increased in the 1990s due to its intense hallucinogenic properties and unregulated status (Boland et al. 2005; EMCDDA 2012). In 1999, 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT), known on the streets as 'foxy' or 'foxy methoxy', began to appear as a party drug and has been increasingly consumed since then (Muller 2004). The abuse problem associated with this substance first emerged in 2001 in the USA (Drug Enforcement Administration 2001) and Japan (Katagi et al. 2002), widening later to many other countries. In turn, the use of 5-methoxy-*N*,*N*-diallyltryptamine (5-MeO-DALT), a tryptamine substitute chemically related to the 5-MeO-DIPT and *N*,*N*-diallyltryptamine (DALT), has been reported only occasionally (Corkery et al. 2012; Jovel et al. 2014).

The emergence of these new 'designer drugs' and the void of information associated with them represent a public health issue and led to the implementation of legislative measures all over the world. Drug legislation varies from country to country and is currently undergoing dynamic changes due to new findings on possible risks for the public health; so, in this review, regulatory aspects are only briefly mentioned. In 2003, the Drug Enforcement Administration (DEA) placed 5-MeO-DIPT and AMT into the Schedule I category through an emergency scheduling provision of the Controlled Substances Act (Drug Enforcement Administration 2003). These substances were formally regulated by DEA in 2004 and were officially listed as Schedule I drugs in 2005 (Drug Enforcement Administration 2004). Currently, in Japan, DMT, *N*,*N*-diethyltryptamine (DET), alpha-ethyltryptamine (AET), psilocin, psilocybin, AMT

and 5-MeO-DIPT are banned substances (Kikura-Hanajiri et al. 2005; Narimatsu et al. 2006). 5-MeO-DALT is controlled in just a few countries around the world, not being presently regulated by international conventions (Corkery et al. 2012). In Portugal, new legislative measures regarding 'designer drugs' were introduced in 2013, penalizing the commercialization and the use of 159 substances, including 13 synthetic tryptamines (Government 2013).

Patterns of use, prevalence and motivation

'Designer drug' packages tend to be very appealing and creative, often using original trade names in an attempt to get the consumers' attention. The real composition of commercial products is often masked, being supplied only minimal information, often incorrectly, and presenting them as harmless. In fact, even substances that are already illegalized have been shown to be included in these products, without the users having the slightest notion of what they are actually consuming and of the legal and health problems they can cause (Ramsey et al. 2010). In order to circumvent the legislative controls, products tend to display advertising messages with warnings like 'not for human consumption' or 'this chemical is only for research use' (Arunotayanun and Gibbons 2012; Kjellgren and Soussan 2011; Musselman and Hampton 2014). Reportedly, it is also noted that the products will only be sold to individuals aged 18 years or older, although in practice this rule is not strictly enforced (Corkery et al. 2012). Tryptamine derivatives are typically sold in the form of tablets or powders, as free base or salt (Alatrash et al. 2006; Corkery et al. 2012). Psilocybin and psilocin, in their pure forms, are sold as white crystalline powders (Tyls et al. 2014). Some tryptamines have characteristic properties, as, for example, the 5-MeO-DALT, described as a powder with a slight smell and a color ranging from white to light brown (Corkery et al. 2012), or the 4-hydroxy-*N*-methyl-*N*-ethyltryptamine (4-OH-MET), which is a white or gray powder with a bitter and sour taste (Kjellgren and Soussan 2011). Several tryptamines can be purchased in small quantities (~500 mg) or in more substantial amounts (e.g., 20 kg) in Internet Web sites (Corkery et al. 2012). Tryptamine prices practiced in Europe can range from 17 to 29€ per gram up to thousands of euros (4600–5400€) per kg, depending on the provider and the type of product that is sought. For US consumers, the prices have been considerably inflated and may even reach values five times higher (Corkery et al. 2012).

A study that has evaluated the 'legal high' products available in the UK online market in 2009 revealed that the most popular products were the stimulants (42 %), sedatives (32 %) and hallucinogens including tryptamines (13 %) (Schmidt et al. 2011). Nevertheless, the compilation of data on the usage prevalence and extent of new psychoactive substances is not done routinely, making it very difficult to establish consumer trends (Hill and Thomas 2011).

In 2009, Björnstad et al. reported that 'magic mushrooms' are widely popular among Swedish users. An analysis of 103 urine specimens, collected over 4 years from young users (average age of 22 years) who were admitted at emergencies on suspicion of ingestion of psychoactive plant materials, revealed that psilocin was the most frequent natural product detected (54 % of the cases) (Bjornstad et al. 2009). In this study, 56 % of the subjects confessed to have acquired the products through the Internet, while others said that they had got them through friends or bought them on the streets (Bjornstad et al. 2009).

A more recent study performed by Maxwell (2014) combined the findings from a variety of databases to characterize the new psychoactive substances users in terms of gender and age. Data showed that tryptamine users tend to be young adults (mean age of 19 years) and male (86 %) and that this kind of consumption affects different races and ethnicities. Some studies also revealed that the use of tryptamine derivatives, especially of 5-MeO-DIPT, has come up very frequent among homosexual drug users (Clatts et al. 2005; Lee et al. 2013; Wada et al. 2013).

Winstock et al. (2014) performed a global study (covering the UK, Australia, USA and the Eurozone countries), through anonymous online surveys conducted between November and December 2012 to a total of 22,289 subjects, aiming to compare DMT prevalence with that of ketamine, LSD and magic mushrooms (psilocybin). The study revealed that the proportion of new consumers of DMT was higher than the one of new users of ketamine, LSD and magic mushrooms, which suggests that DMT is an increasingly popular substance for those looking for an alternative to traditional hallucinogens (Winstock et al. 2014).

In Australia, an online survey to study the consumption patterns of DMT was performed with 121 participants that used DMT at least once in their lifetime. Most consumers were male (86 %) with a mean age of 28 years. The median age of onset of DMT consumption was 24 years. Sixty percent of participants had completed the university, and only 11 % of respondents were unemployed. The most frequent source of information about DMT came from friends, the Internet and media, respectively. The median total number of DMT consumption per participant was ten times, preferably smoked (98 %). Apart from DMT, participants also reported to be consumers of other hallucinogens, including LSD (97 %) and psilocybin mushrooms (92 %) (Cakic et al. 2010).

Despite the worldwide prevalence of tryptamines being virtually unknown, it is certain that their popularity and consequent consumption have been increasing, and there

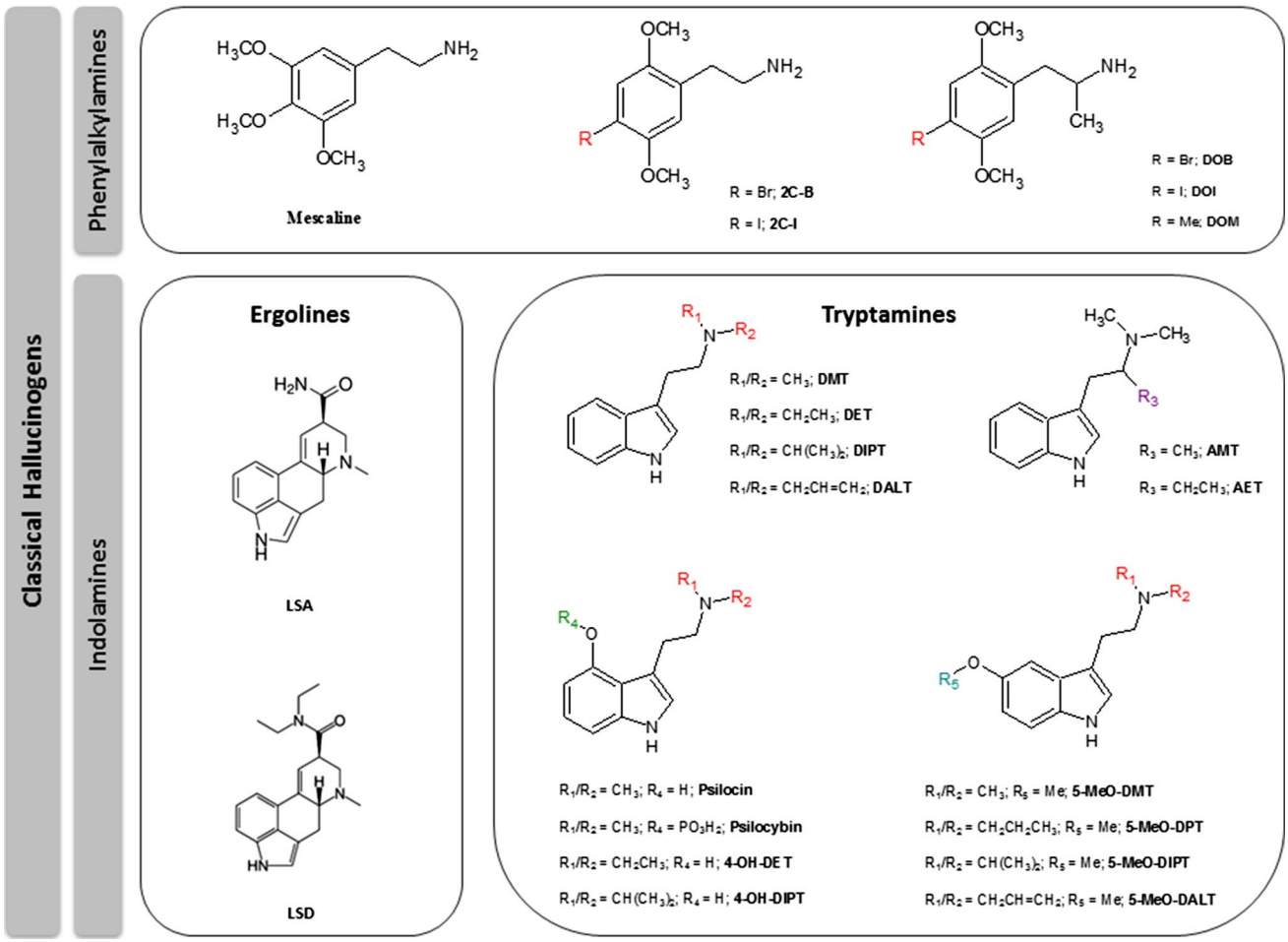


Fig. 2 Chemical structures of most representative serotonergic hallucinogens. The wide variety of synthetic tryptamine analogs may exhibit different modifications on the nitrogen atom of the side chain (indicated in *red*), on the α position of the side chain (highlighted in *purple*) and/or in the aromatic ring (modifications at the 4-position are indicated in *green*, while at the 5-position are shown in *blue*) (color figure online)

are many factors that can explain this phenomenon. This rapid expansion seems to be linked to their wide availability and easy acquisition in 'headshops', raves and nightclubs, or through the Internet, associated with the reduced accessibility to traditional LSD (Babu et al. 2005; Jovel et al. 2014; Musselman and Hampton 2014; Sanders et al. 2008). Furthermore, many tryptamines do not have a scheduled status, have a lower price as compared to illicit classical drugs (3€ per dose compared to 9€ for LSD, in Europe), and their molecular structure allowed users to elude routine clinical drug testing, thus making them more accessible and desirable (EMCDDA 2010; Jovel et al. 2014; Musselman and Hampton 2014). Generally, users of synthetic tryptamines referred their curiosity about these new psychoactive substances and the desire to experience new mental states as their main motivations, being these reasons stronger than any void of information that is associated with this type of psychotropic substances (Cakic et al. 2010; Kjellgren and Soussan 2011).

Chemistry

In general, classical hallucinogens can be divided into two main structural classes: phenylalkylamines and indolamines (Fig. 2). The chemical backbone of hallucinogenic phenylalkylamines is a phenethylamine group, which is a prevalent structure in a range of endogenous compounds, including the neurotransmitters dopamine and norepinephrine (Fantegrossi et al. 2008a). The naturally occurring compound mescaline, an alkaloid isolated from Peyote cactus (*Lophophora williamsii*), or the synthetic compounds 2,5-dimethoxy-4-methylamphetamine (DOM) and 2,5-dimethoxy-4-iodoamphetamine (DOI) are examples of this class of hallucinogens. By contrast, indolamines contain an indole nucleus as basic structure, having a high structural similarity with 5-hydroxytryptamine (5-HT or serotonin), a monoamine neurotransmitter that modulates human mood and behavior. 5-HT is the simplest of all known tryptamines, differing only in the absence of a

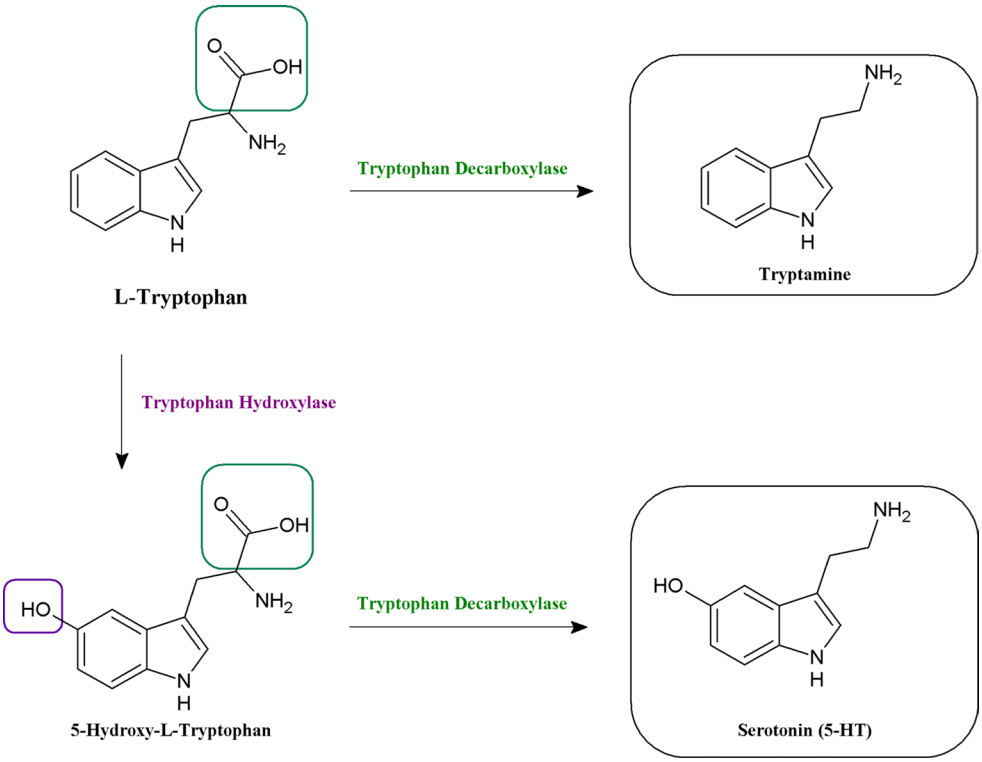


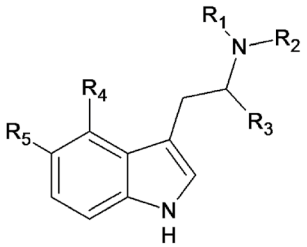
Fig. 3 Endogenous formation of tryptamine and the neurotransmitter serotonin

hydroxyl group on the aromatic ring (Fantegrossi et al. 2008a; Gibbons 2012). This similarity is undoubtedly due to the fact that they have in common the amino acid tryptophan as the starting point for their synthesis, as illustrated in Fig. 3 (Brandt et al. 2004).

Indolamines can be subclassified into two main groups (Fig. 2): (1) the simple tryptamines (including substances like DMT and psilocybin) that can be subdivided according to the site of the modification and (2) the ergolines such as LSD (Fantegrossi et al. 2008a; Hill and Thomas 2011; Nichols 2004). The ergolines have a complex and relatively rigid structure with an indole system and a tetracyclic ring (Fantegrossi et al. 2008a; Hill and Thomas 2011; Nichols 2004). In turn, simple tryptamines have a bicyclical combination of benzene and a pyrrole ring (indole ring structure) combined to an amine group by a two-carbon side chain. The huge variety of synthetic tryptamine analogs may exhibit different modifications on the α position of the ethylamine side chain, on the nitrogen atom of side chain and/or in the aromatic ring, as depicted in Table 1 and Fig. 2 (Fantegrossi et al. 2008a; Gibbons 2012; Hill and Thomas 2011; Nichols 2004). Some hallucinogenic tryptamines, such as AMT and AET, only contain an α-alkyl substituent. Tryptamines such as DMT, DALT, DET, *N*,*N*-diisopropyltryptamine (DIPT) and *N*,*N*-dipropyltryptamine (DPT) have no substituents on the aromatic ring, but show modifications on the nitrogen atom of the side chain. Tryptamine derivatives that present a substitution on position 4 of the indole ring include substances such as psilocybin, psilocin, 4-hydroxy-*N*,*N*-diethyltryptamine (4-OH-DET), 4-hydroxy-*N*,*N*-diisopropyltryptamine (4-OH-DIPT), 4-hydroxy- *N*-methyl-*N*-isopropyltryptamine (4-OH-MIPT), 4-acetoxy-*N*,*N*-diethyltryptamine (4-AcO-DET) or 4-acetoxy-*N*,*N*-diisopropyltryptamine (4-AcO-DIPT). In turn, tryptamines that have substitutions in the 5-position of the aromatic ring include substances such as 5-MeO-DMT, 5-MeO-DIPT and 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MIPT, also known as 'moxy'). Information related to tryptamines that have substitutions at positions 6 or 7 of the indole ring are scarce.

Different structural modifications gave rise to diverse molecules with dissimilar chemical properties, which consequently have the ability to induce different states of mind and behaviors. The principal structural feature that gives the hallucinogenic properties to tryptamine analogs is the indole nucleus (Freeman and Alder 2002). Although the double-ring structure presents seven positions where modifications are possible, the majority of the modifications occur essentially at positions 4 or 5 since modifications at positions 6 and 7 have been described as originating compounds with reduced hallucinogenic activity (Hill and Thomas 2011; Rogawski and Aghajanian 1981). The introduction of a hydroxyl or methoxy group at positions 4 and 5, respectively, is associated with increased potency of tryptamine derivatives as compared to analogs with substitutions at different positions (Rogawski and Aghajanian 1981). When

Table 1 Chemical structures of known natural and synthetic tryptamines used as drugs of abuse



Common Name	Chemical name	R_1	R_2	R_3	R_4	R_5
Tryptamine	**Tryptamine**	**H**	**H**	**H**	**H**	**H**
AET	α-Ethyltryptamine	H	H	CH_2CH_3	H	H
AMT	α-Methyltryptamine	H	H	CH_3	H	H
Bufotenine	5-Hydroxy-*N,N*-dimethyltryptamine, 5-OH-DMT	CH_3	CH_3	H	H	OH
DALT	*N,N*-diallyltryptamine	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	H	H
DBT	*N,N*-dibutyltryptamine	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	H	H	H
DET	*N,N*-diethyltryptamine	CH_2CH_3	CH_2CH_3	H	H	H
DIPT	*N,N*-diisopropyltryptamine	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	H
DMT	*N,N*-dimethyltryptamine	CH_3	CH_3	H	H	H
DPT	*N,N*-dipropyltryptamine	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	H
EIPT	*N*-ethyl-*N*-isopropyltryptamine	CH_2CH_3	$CH(CH_3)_2$	H	H	H
MIPT	*N*-methyl-*N*-isopropyltryptamine	CH_3	$CH(CH_3)_2$	H	H	H
MPT	*N*-methyl-*N*-propyltryptamine	CH_3	$CH_2CH_2CH_3$	H	H	H
NMT	*N*-methyltryptamine	H	CH_3	H	H	H
Psilocin	4-Hydroxy-*N,N*-dimethyltryptamine, 5-OH-DMT	CH_3	CH_3	H	OH	H
Psilocybin	4-Phosphoryloxy-*N,N*-dimethyltryptamine	CH_3	CH_3	H	OPO_3H_2	H
4-AcO-DET	4-Acetoxy-*N,N*-diethyltryptamine	CH_2CH_3	CH_2CH_3	H	$OCOCH_3$	H
4-AcO-DIPT	4-Acetoxy-*N,N*-diisopropyltryptamine	$CH(CH_3)_2$	$CH(CH_3)_2$	H	$OCOCH_3$	H
4-OH-DBT	4-Hydroxy-*N,N*-dibutyltryptamine	$CH_2CH_2CH_2CH_3$	$CH_2CH_2CH_2CH_3$	H	OH	H
4-OH-DET	4-Hydroxy-*N,N*-diethyltryptamine	CH_2CH_3	CH_2CH_3	H	OH	H
4-OH-DIPT	4-Hydroxy-*N,N*-diisopropyltryptamine	$CH(CH_3)_2$	$CH(CH_3)_2$	H	OH	H
4-OH-DPT	4-Hydroxy-*N,N*-dipropyltryptamine	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	OH	H
4-OH-MET	4-Hydroxy-*N*-methyl-*N*-ethyltryptamine	CH_2CH_3	CH_3	H	OH	H
4-OH-MIPT	4-Hydroxy-*N*-methyl-*N*-isopropyltryptamine	CH_3	$CH(CH_3)_2$	H	OH	H
4-OH-MPT	4-Hydroxy-*N*-methyl-*N*-propyltryptamine	CH_3	$CH_2CH_2CH_3$	H	OH	H
4-MeO-MIPT	4-Methoxy-*N*-methyl-*N*-isopropyltryptamine	CH_3	$CH(CH_3)_2$	H	OCH_3	H
5-MeO-AMT	5-Methoxy-α-methyltryptamine	H	H	CH_3	H	OCH_3
5-MeO-DALT	5-Methoxy- *N,N*-diallyltryptamine	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	H	OCH_3
5-MeO-DET	5-Methoxy-*N,N*-diethyltryptamine	CH_2CH_3	CH_2CH_3	H	H	OCH_3
5-MeO-DIPT	5-Methoxy- *N,N*-diisopropyltryptamine	$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	OCH_3
5-MeO-DMT	5-Methoxy-*N,N*-dimethyltryptamine	CH_3	CH_3	H	H	OCH_3
5-MeO-DPT	5-Methoxy-*N,N*-dipropyltryptamine	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	H	OCH_3
5-MeO-EIPT	5-Methoxy-*N*-ethyl-*N*-isopropyltryptamine	CH_2CH_3	$CH(CH_3)_2$	H	H	OCH_3
5-MeO-MIPT	5-Methoxy-*N*-methyl-*N*-isopropyltryptamine	CH_3	$CH(CH_3)_2$	H	H	OCH_3
5-MeO-NMT	5-Methoxy-*N*-methyltryptamine	CH_3	H	H	H	OCH_3

the modifications in the aromatic ring are combined with substitutions on the side chain with the addition of the 2-aminoethyl or 2-aminopropyl group, the psychotropic effect is considered maximal (Freeman and Alder 2002). Shulgin and Shulgin (1997) described modifications in the activity following oral intake in humans when tryptamines present amine substitutions with methyl, ethyl and propyl groups in any combination and revealed

that alkyl-*N*-substituted homologs with longer chains, such as dibutyltryptamine (DBT), are unaffected by MAO degradation, being orally active. However, Shulgin and Shulgin (1997) also described that the potency of these derivatives with a long alkyl chain is lower. Increased lipophilicity, with introduction of the α-methyl group, may also be a factor for an increase in activity due to increased blood–brain barrier permeability (Shulgin and Shulgin 1997). Unsubstituted primary amine tryptamines tend to be orally inactive because they are metabolized by MAO (Shulgin and Shulgin 1997). However, based on user reports, all known tryptamine derivatives have oral activity with the exception of DMT (Ott 1999, 2001a, b). Hydroxyl substitution in the indole ring can provide varied properties with some derivatives being hallucinogenic, while others may have no psychoactivity (Shulgin and Shulgin 1997).

The synthetic routes to achieve these new compounds are relatively simple, with the information for its creation easily available on the Internet (e.g., drug libraries like www.erowid.org), giving to everyone an easy access to the synthesis of potential hallucinogenic drugs (Brandt et al. 2004; Brush et al. 2004).

Toxicokinetics

Routes of administration, typical doses and duration of effects

The Psilocybe mushrooms users typically consume the mushrooms eating them raw or preparing tea, by steeping fresh or dry biomass in hot water in order to improve the extraction of active principles (Arunotayanun and Gibbons 2012). In turn, the synthetic tryptamines may be consumed by a set of known routes of administration, including insufflation (snorting, sniffing), inhalation (smoking), intravenous or intramuscular injection, orally (swallowing in a capsule, wrapped in a cigarette paper or in combination with a drink) or rectally, depending on the substance and user (Corkery et al. 2012; Drugs Forum 2010; Hill and Thomas 2011).

User reports indicate that the most common route of administration for 4-OH-MET is oral, but the nasal route can be used too (Kjellgren and Soussan 2011). 5-MeO-DIPT ('foxy') can be administered orally or by intranasal route (Babu et al. 2005; Muller 2004), while oral route is the main form of administration for 5-MeO-DALT (Corkery et al. 2012). DMT is not orally active due to extensive first-pass metabolism, probably through the rapid action of MAO enzymes in the gut and liver, and is therefore typically used by inhalation or insufflation, the typically routes described for the 5-MeO-DMT too (Babu et al. 2005; Cakic et al. 2010; Cunningham 2008; McKenna 2004; Nelson et al. 2014; Nichols 2004). This is extremely relevant since users can intentionally consume MAO inhibitors in order to enhance the activity of substances such as DMT that otherwise would be orally inactive. As mentioned previously (see section "The evolution in the use of tryptamines: from natural substances to synthetic drugs"), an example of this combination is the beverage ayahuasca (Cunningham 2008; McKenna 2004). However, this association with MAO inhibitors may be even more complex because this kind of potentiators, as in the case of some β-carboniles, may be neurologically active too (Freeman and Alder 2002); moreover, some tryptamines are converted to substitutes β-carboniles in the human body (Musshoff et al. 1996) and are also present in some foodstuffs such as beers and wines (Gutsche et al. 1999; Tsuchiya et al. 1996). In contrast, the amine nitrogen alkyl substituents in DMT result in homologs, such as DET, DPT, DIPT and *N*-methyl-*N*-isopropyltryptamine (MIPT), that are orally active, being the preferential route of administration (Halberstadt and Geyer 2013).

The dose of tryptamine derivatives and duration of their effects commonly differ among compounds and depend on their potency and route of administration. As described in a previous section, the presence of a 4-hydroxy or a 5-methoxy substituent on the indole ring considerably increases the potency of *N*,*N*-dialkyltryptamines, and therefore, lower doses are required for obtaining effects with these tryptamines when compared with their unsubstituted parent compounds (Freeman and Alder 2002; Rogawski and Aghajanian 1981).

Psilocybin is described as 45 times less potent than LSD (Isbell 1959), and the typical oral dose per adult is above 15 or 1–2 mg when administered intravenously (i.v.) (Arunotayanun and Gibbons 2012; Cunningham 2008; Hasler et al. 2004; Tyls et al. 2014). The onset of effects for psilocybin is around 20–40 min, lasting 4–6 h after oral administration (Hasler et al. 2004). In relation to the i.v. administration, the effects begin more quickly (1–2 min) but have a much shorter duration (only about 20 min) (Hasler et al. 1997). In turn, as for psilocin in its pure form, oral doses may vary between 6 and 20 mg, inducing a rapid onset of effects that can last 4–8 h (Hill and Thomas 2011). The amount of psilocybin per mushroom is variable, and therefore, the amount needed to produce desired effects is also flexible, despite users reporting two to six mushrooms as sufficiently effective (Cunningham 2008).

The typical oral doses of 5-MeO-DALT range from 12 to 25 mg (Shulgin and Shulgin 1997), although doses

over 50 mg have been reported (Corkery et al. 2012). The main effects of this substance seem to be dose dependent, with onset of expected effects around 15 min after being taken orally and duration of action between 2 and 4 h, although the visual disturbance may persist for a longer period (Corkery et al. 2012). The same pattern is reported to 4-OH-MET, with the 25 mg indicated as the most common oral dosage, although there are reports that claim the ingestion of higher amounts (up to 180 mg) (Kjellgren and Soussan 2011; Shulgin and Shulgin 1997). The duration of effects estimated for the 4-OH-MET is 4–6 h for oral administration (Kjellgren and Soussan 2011).

The hallucinogenic effects of ayahuasca usually appear within 1 h after its oral consumption and can last about 4 h (Cakic et al. 2010). In contrast to oral administration, the effects of smoked DMT are extremely intense and emerge rapidly but last <30 min (Strassman 2001; Turner 1994). In contrast, when smoked, 5-MeO-AMT can persist up to 12 h (Babu et al. 2005). The rapid effects of DMT by this route of administration contrast significantly with the long duration of LSD effects (8–12 h) (Rothlin 1957) by which the DMT was coined the 'businessman's lunch trip' (Turner 1994). Typical doses of DMT are 40–50 mg when smoked, but some reports describe doses up to 100 mg (Shulgin and Shulgin 1997), and for i.v. administration, dosages can be reduced, ranging between 0.1 and 0.4 mg/kg (Strassman et al. 1996). In contrast, its 5-methoxy analog (5-MeO-DMT) is active at considerably lower doses (3–5 mg) when smoked or administered parenterally (Halberstadt and Geyer 2013).

Metabolic pathways

Drug metabolism studies with indolamine hallucinogens including LSD, psilocybin, DMT, 5-MeO-DMT and 5-MeO-DIPT have been performed mainly in laboratory animals (Erspamer 1955; Kanamori et al. 2006; Siddik et al. 1979) and, more recently, also in man (Hasler et al. 2002; Kamata et al. 2006; McIlhenny et al. 2011, 2012; Meatherall and Sharma 2003; Riba et al. 2012; Sklerov et al. 2000; Sticht and Kaferstein 2000; Wilson et al. 2005). However, it must be highlighted that almost nothing is known for many other tryptamine analogs regarding their metabolic pathways or the contribution of specific enzymes to their biotransformation. Based on those limited metabolic studies, data suggest that not all tryptamines share a common metabolic pathway, varying upon the nature and position of substituents in the molecules.

Following absorption, tryptamine analogs undergo phase I and phase II metabolism. The ergoline LSD is extensively metabolized and <1 % of the ingested dose is eliminated unchanged in urine. Major metabolites detected in the rat and guinea pigs urine were the 13- and 14-hydroxy-LSD and their corresponding glucuronide conjugates (Siddik et al. 1979). Other metabolites included 2-oxo-LSD, lysergic acid ethylamide and *N*-desmethyl-LSD. However, significant differences in LSD metabolism between laboratory animals and humans have been observed. In fact, the analysis of urine from LSD users identified five metabolites, namely the 2-oxo-LSD, 2-oxo-3-hydroxy-LSD, *N*-desmethyl-LSD, 13- and 14-hydroxy-LSD glucuronides (Fig. 4) (Poch et al. 1999; Reuschel et al. 1999; Sklerov et al. 2000). The 2-oxo-3-hydroxy-LSD showed to be a major human urinary metabolite with concentrations several times greater than LSD itself (Poch et al. 1999, 2000; Reuschel et al. 1999; Sklerov et al. 2000). In vitro studies in human liver microsomes and hepatocytes confirmed the formation of 2-oxo-3-hydroxy-LSD, being 2,3-dihydroxy-LSD also identified (Klette et al. 2000), suggesting that 2-oxo-3-hydroxy-LSD could be produced through dehydrogenation of the 2,3-dihydroxy-LSD intermediate, which is presumably formed from LSD 2,3-epoxide. The contribution and importance of specific metabolizing enzymes in the formation of the LSD main metabolites, such as 2-oxo-3-hydroxy-LSD, remain hitherto unclear.

Different from LSD, psilocybin (a 4-substituted indolamine) is rapidly dephosphorylated by phosphatases in the digestive tract, in kidney and probably in the human blood to generate its pharmacologically active metabolite psilocin. Oxidative deamination of psilocin to form 4-hydroxyindole acetic acid (4-OH-IAA) constitutes a minor metabolic pathway (Hasler et al. 2002; Horita and Weber 1961; Sticht and Kaferstein 2000). Psilocin is further metabolized by phase II enzymes to give the psilocin-*O*-glucuronide, which is the main metabolite detected in human urine (Hasler et al. 2002; Horita and Weber 1961; Sticht and Kaferstein 2000). The main metabolic pathways of psilocybin are shown in Fig. 5. In spite of these data, limited studies on the metabolism of psilocybin and psilocin have been reported, and specific enzymes that catalyze the formation of individual metabolites remain unknown.

Like 5-HT itself, some tryptamine derivatives including DMT, 5-OH-DMT and 5-MeO-DMT are well known to be extensively metabolized through oxidative deamination to their corresponding indole acetic acid (IAA) derivatives mediated by monoamine oxidase A (MAO-A) (Sitaram et al. 1987b). Metabolic studies performed in rats showed that 3-IAA and 3-indole-aceturic acid are the main urinary metabolites of DMT (Erspamer 1955). The absence of unchanged DMT in the urine and the rapid disappearance of DMT in plasma (Erspamer 1955; Kaplan et al. 1974; Szara 1956) suggest that drug metabolism occurs extremely

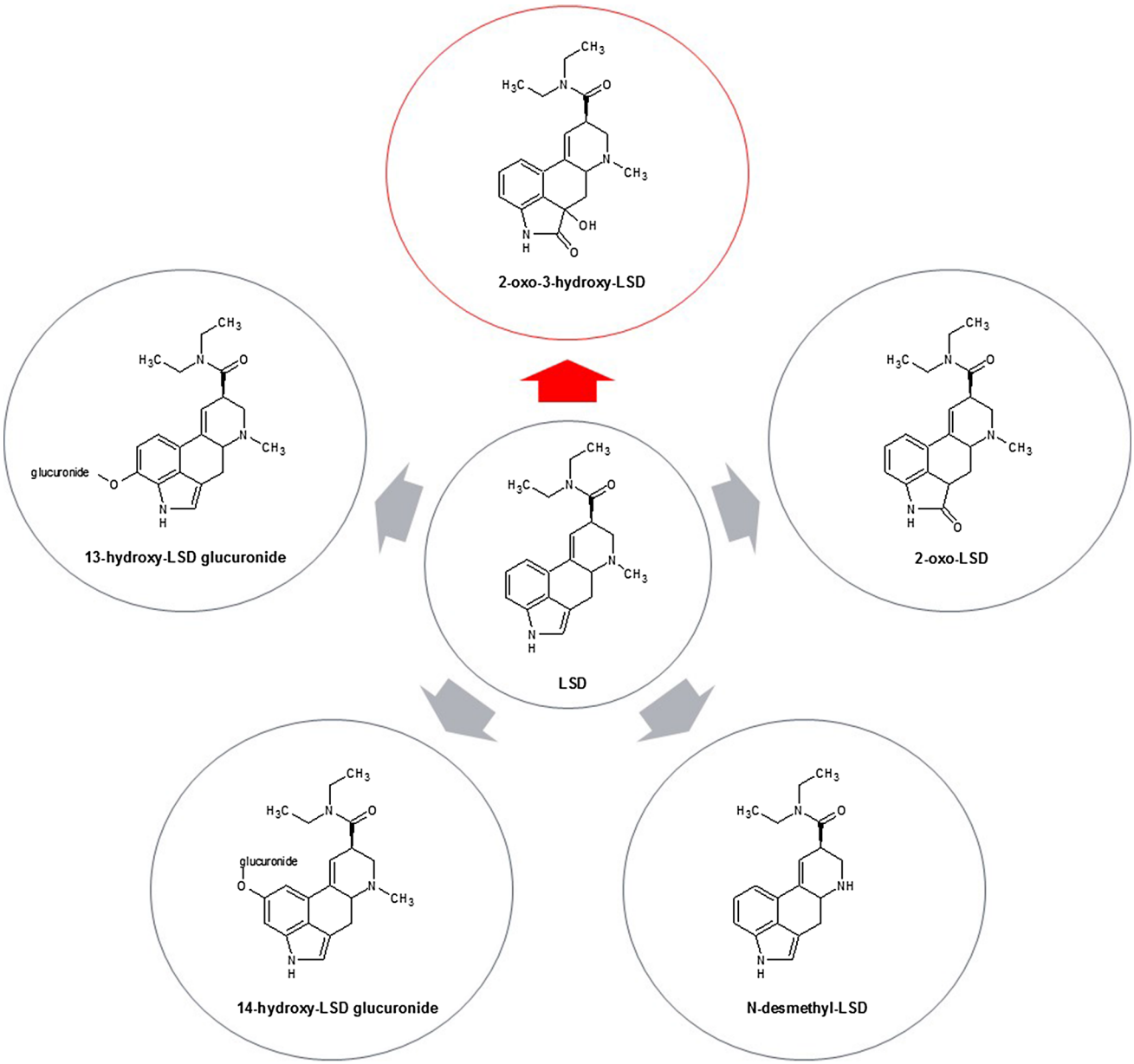


Fig. 4 Metabolites of LSD identified in human urine. The 2-oxo-3-hydroxy-LSD (highlighted in *red*) is the major metabolite (color figure online)

fast and might explain the reported lack of psychoactive effects following DMT oral intake.

MAO-catalyzed oxidative deamination is not the only metabolic pathway, as in vitro and in vivo studies have described alternative biotransformation routes, namely *N*-oxidation, *N*-demethylation and cyclization (Barker et al. 1980; Fish et al. 1955b; McIlhenny et al. 2011, 2012; Riba et al. 2012; Sitaram and McLeod 1990). The DMT-*N*-oxide (DMT-NO) was found in significant concentrations in the human urine and blood (McIlhenny et al. 2011, 2012; Riba et al. 2012) following oral administration of ayahuasca and does not appear to be a substrate for MAO (Fish et al. 1955b; Sitaram et al. 1987a). *N*-methyltryptamine (NMT), 2-methyl-1,2,3,4-tetrahydro-beta-carboline (2-MTHBC) and 1,2,3,4-tetrahydro-beta-carboline (THBC) were identified as minor metabolites of DMT (Barker et al. 1980; Sitaram and McLeod 1990). The *N*-demethylated metabolite (NMT) is also a substrate for MAO and is likely to be further metabolized to IAA. The metabolic routes leading to each metabolite are depicted in Fig. 6. 5-MeO-DMT appears to be metabolized by essentially the same routes as described for DMT (Shen et al. 2010; Sitaram et al. 1987a, b).

As mentioned previously, DMT and 5-MeO-DMT are often used in combination with MAO-A inhibitors such

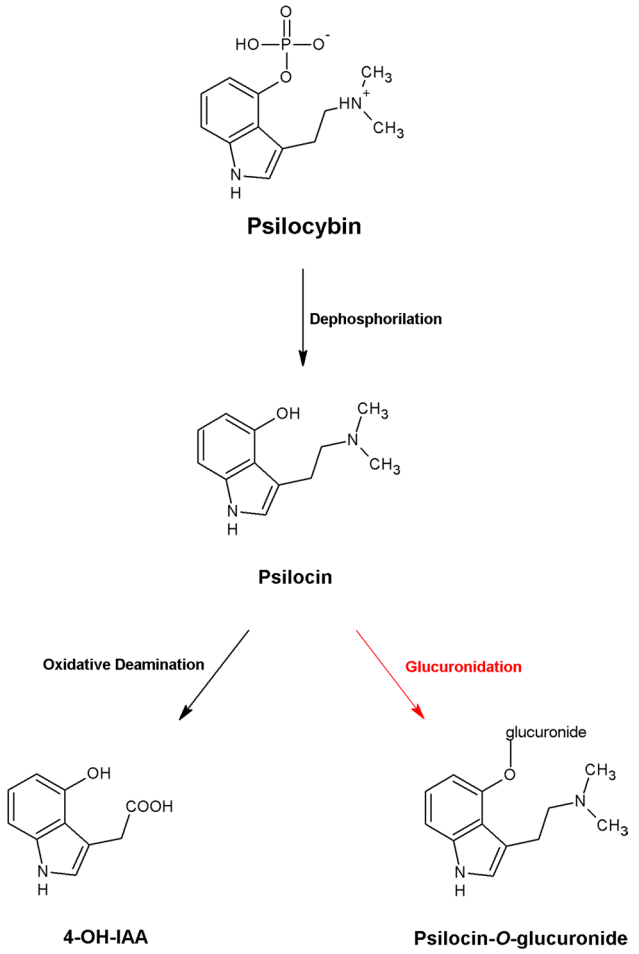


Fig. 5 Metabolic pathways for psilocybin in humans. Oxidative deamination of psilocin to form 4-hydroxyindole acetic acid (4-OH-IAA) constitutes a minor metabolic pathway, while the glucuronidation (indicated by a *red arrow*) is the major metabolic route (color figure online)

as ayahuasca β-carbolines (e.g., harmine and harmaline) (Kim et al. 1997; McKenna et al. 1984), and under this setting, MAO-mediated deamination pathway is reduced, thus increasing exposure to the parent tryptamine and, subsequently, escalating drug effects. Recently, Riba et al. (2014, 2012) identified the DMT metabolites in urine of humans after oral ingestion of DMT alone and in ayahuasca preparation, and also when DMT is smoked. DMT by itself had no psychotropic effects, and no DMT was recovered in urine. When DMT was ingested alone, no DMT was recovered in urine, the MAO-dependent metabolite, 3-IAA, represented 97 % of the recovered compounds, whereas DMT-NO accounted for only 3 % (Riba et al. 2014). In turn, when administered together with the β-carbolines in ayahuasca, DMT was fully psychoactive and <1 % of the administered DMT dose was excreted unchanged. IAA levels dropped to 50 %, DMT-NO rose to 10 %, and NMT and 2-MTHBC were detected as minor metabolites (Riba et al. 2012). The authors argue that MAO inhibition in the presence of ayahuasca may be either incomplete or short-lived, as large amounts of IAA were already found in the first 4 h after ayahuasca intake. Moreover, despite the only partial inhibition of MAO afforded by the presence of β-carbolines in ayahuasca, it was sufficient to allow drug central effects. Similar to what was observed after ayahuasca administration, smoked DMT exhibited psychoactive effects and unmetabolized DMT (10 %) was found in urine together with around 63 % IAA and 28 % DMT-NO (Riba et al. 2014). Together, these data indicate that in the smoked route or when MAO is inhibited a shift from MAO dependent to cytochrome P450 (CYP) enzyme-dependent metabolism occurs. This shift has also been observed in in vitro and in vivo studies with the MAO inhibitor iproniazid (Sitaram et al. 1987b).

The metabolism of 5-MeO-DIPT ('foxy'), a recently abused tryptamine derivative that contains *N*,*N*-diisopropyl groups instead of the *N*,*N*-dimethyl groups within DMT, was also recently characterized in urine samples from users. As depicted in Fig. 7, three major phase I metabolic pathways were proposed in humans: the *O*-demethylation to 5-hydroxy-*N*,*N*-diisopropyltryptamine (5-OH-DIPT); the direct hydroxylation on position 6 of the aromatic ring and/or methylation of the hydroxyl group on position 5 after hydroxylation on position 6 of the aromatic ring of 5-OH-DIPT to produce 6-hydroxy-5-methoxy-*N*,*N*-diisopropyltryptamine (6-OH-5-MeO-DIPT); and side chain degradation by *N*-dealkylation to the corresponding secondary amine 5-MeO-NIPT (Kamata et al. 2006; Meatherall and Sharma 2003; Wilson et al. 2005). Quantitative data revealed that the hydroxylated metabolites were detected in greatest abundance and may still undergo phase II reactions, being partially eliminated as sulfate or glucuronide conjugates (Kamata et al. 2006). Kinetic and inhibitory in vitro studies using pooled human liver microsomes unveiled that CYP2D6 is responsible for 5-MeO-DIPT *O*-demethylation, CYP1A1 for hydroxylation to 6-OH-5-MeO-DIPT, while isoenzymes CYP2C19, 1A2 and 3A4 (CYP2C19 > CYP1A2 > CYP3A4 > CYP2C8 > CYP2C9 = CYP2D6) mediate *N*-dealkylation (Narimatsu et al. 2006). *In vivo* studies performed in rats revealed a similar metabolic profile with 5-hydroxy-*N*-isopropyltryptamine (5-OH-NIPT), 5-methoxyindole-3-acetic acid (5-MeO-IAA), 5-MeO-NIPT and 5-OH-DIPT identified as metabolites, being the last one the main metabolite of 5-MeO-DIPT in the rat (Kanamori et al. 2006). Noteworthy, in vitro studies using rat liver microsomes showed that functional CYP enzymes involved in the 5-MeO-DIPT rat metabolism are different from those identified in humans: CYP2D6, 2C6 and 1A1 exhibited considerable *O*-demethylation activity, CYP2C11, 1A2, 2C6 and 3A2 showed to

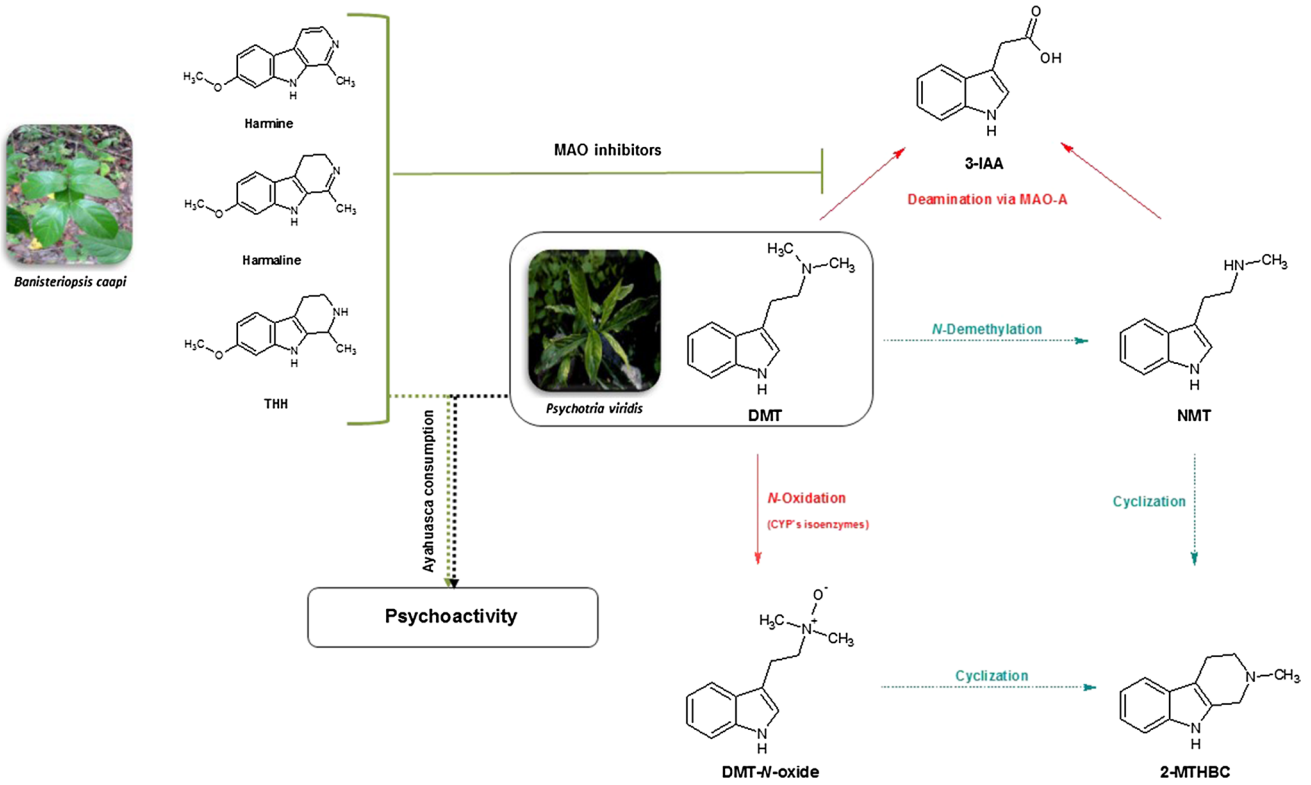


Fig. 6 Major (*red arrows*) and minor (*blue arrows*) metabolic pathways for *N*,*N*-dimethyltryptamine (DMT) in humans. The interaction between DMT and β-carbonile derivatives is also illustrated. After oral consumption, DMT is rapidly inactivated by MAO enzymes in liver and gut. In contrast, when DMT is taken combined with MAO inhibitors, such as β-carbolines present, for example, in *Banisteriopsis caapi* plant, this process is partly blocked and DMT exerts its hallucinogenic effects. The hallucinogenic brew *ayahuasca* reflects perfectly this interaction. 3-IAA, indole-3-acetic acid; 2-MTHBC, 2-methyl-1,2,3,4-tetrahydro-beta-carboline; NMT, *N*-methyltryptamine; THH, tetrahydroharmine (color figure online)

catalyze the side chain *N*-dealkylation, while CYP1A1 also exhibited 5-MeO-DIPT-6-hydroxylase activity as occurs in humans (Narimatsu et al. 2008).

Similar metabolic pathways to those of 5-MeO-DIPT were described for 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MIPT) in humans (Kamata et al. 2010) and are also shown in Fig. 7.

Toxicodynamics

Receptor interactions

The discovery of serotonin in the brain occurred in 1953 (Twarog and Page 1953) just a few years before the synthesis of LSD was accomplished, being quickly noticed the chemical similarity between these two substances. Anden et al. (1968) were the first authors to disclose that LSD and 5-hydroxytryptophan (the 5-HT precursor) produced similar effects in rat spinal cord and brain, suggesting that LSD stimulates central 5-HT receptors. Later, Marek and Aghajanian (1996) developed electrophysiological studies showing that LSD acts as partial agonist at 5-HT_{2A} receptors on a subpopulation of gamma-aminobutyric acid (GABA) interneurons in layer III of the rat piriform cortex, consistent with the former theory.

Despite their chemical differences, phenylalkylamine and indolamine hallucinogens produce remarkably similar effects in animals and humans, clearly distinct from the effects caused by other classes of drugs of abuse as cannabinoids or amphetamines (Isbell 1959; Shulgin and Shulgin 1997; Wolbach et al. 1962). This similarity of effects and their ability to produce cross-tolerance (Wolbach et al. 1962) indicate that both hallucinogenic classes act through the same receptors. Glennon et al. (1984) and Titeler et al. (1988) soon discovered a high correlation between the affinity to receptors 5-HT_2 and hallucinogenic potency in humans. Radioligand binding studies showed that phenylalkylamine hallucinogens such as mescaline are typically selective for 5-HT_2 receptors, including the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes (Pierce and Peroutka 1989; Titeler et al. 1988). Like phenylalkylamines, the tryptamine hallucinogens such as LSD, psilocin, DMT or 5-MeO-DMT act as 5-HT_2 receptor agonists, but they are much

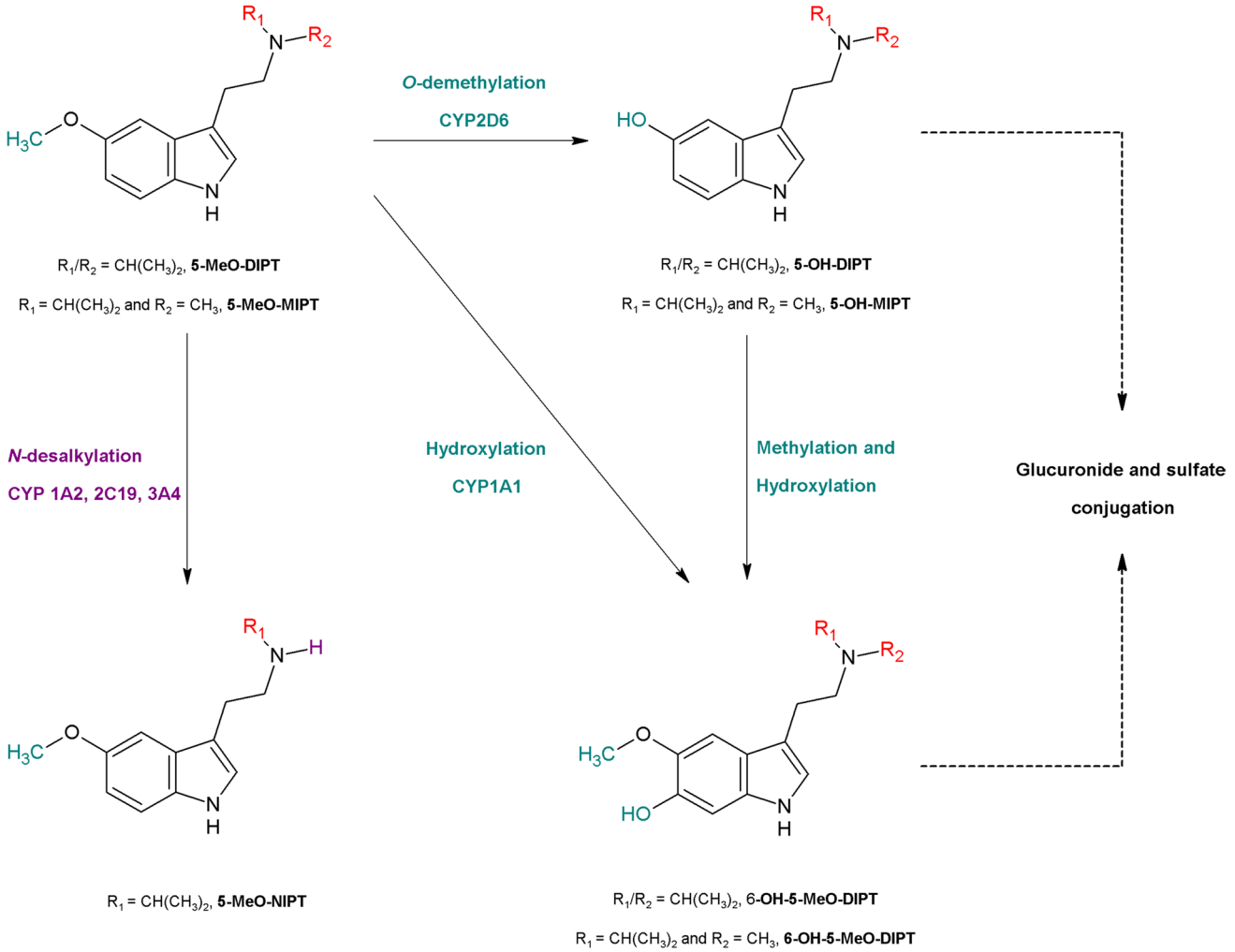


Fig. 7 Proposed metabolic pathways for 5-MeO-DIPT and its analog 5-MeO-MIPT in humans

less selective, binding to a variety of 5-HT_1 and 5-HT_2 receptor subtypes (including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{2A} and 5-HT_{2C} receptors) with different affinities (Blair et al. 2000; Fantegrossi et al. 2006, 2008a; McKenna et al. 1990; Peden et al. 1981; Strassman et al. 1996; Winter et al. 2000). For example, N_1-n-propyl-5-methoxy-α-methyltryptamine binds preferentially at 5-HT_2 receptors (Glennon et al. 1990), while 5-MeO-DIPT has a considerably increased affinity for 5-HT_{1A} receptors, although it also has affinity for 5-HT_{2A} and 5-HT_{2C} receptors (Fantegrossi et al. 2006). Derivatives without ring substituents exhibited lower affinities to all recognition sites when compared to derivatives with substitutions at the 4- or 5-position of the indole ring (McKenna et al. 1990).

Despite their promiscuous binding profile, tryptamine derivatives, in general, exert their effects by binding to and activating primarily the serotonin 5-HT_{2A} receptor, being the main responsible for mediating the effects of hallucinogens in human subjects as well as in animal behavioral paradigms, as described in next subsections (Fantegrossi et al. 2006, 2008a; Halberstadt and Geyer 2011; McKenna et al. 1990). Notwithstanding, many tryptamines bind and activate non-serotonergic receptors as well (Fantegrossi et al. 2008a; Nagai et al. 2007). DMT is described as sigma-1 (σ1) receptor agonist with moderate affinity (Fontanilla et al. 2009), although this is not its main interaction, since DMT affinity for 5-HT_{1A} and 5-HT_{2A} receptors is twice greater than for σ1 (Halberstadt and Geyer 2011). Furthermore, other substances such as cocaine have no hallucinogenic properties, but also bind to the σ1 receptor, emphasizing the fact that σ1 activation by DMT does not have a main role in mediating its hallucinogenic effects (Halberstadt and Geyer 2011). DMT and some of its derivatives are also a ligand to the trace amine-associated receptors (TAAR) (Bunzow et al. 2001) and are substrates for the vesicular monoamine transporter 2 (VMAT2) (Cozzi et al. 2009) and serotonin transporter (SERT) (Cozzi et al. 2009; Nagai et al. 2007). Although LSD and other ergoline

hallucinogens display high affinity for 5-HT receptors, it appears that dopaminergic and adrenergic receptors play an additional role in mediating certain aspects of the behavioral effects provoked by these compounds (Halberstadt and Geyer 2011).

Behavioral and physiological studies in animals

Due to ethical restrictions, very few human clinical trials using hallucinogenic drugs have been conducted and, therefore, animal behavior models have been the main methodology used to study their effects in vivo. The drug discrimination paradigm is a valuable tool to study the activity of psychoactive drugs. Hirschhorn and Winter (1971) demonstrated for the first time that trained rats have the ability to discriminate the interoceptive stimulus evoked by mescaline and LSD from a saline solution used as control. Later, it was shown that many other classical hallucinogens such as DOI (Glennon 1986; Smith et al. 2003), DOB (Glennon et al. 1987), DOM (Li et al. 2008), psilocybin (Koerner and Appel 1982), DMT (Gatch et al. 2009), DPT (Fantegrossi et al. 2008b) and 5-MeO-DMT (Glennon et al. 1979) are also able to function as discriminative stimuli in drug discrimination studies. All these training drugs produced cross-generalization, suggesting that they evoke similar interoceptive stimulus cues. Drug discrimination studies in rats trained to distinguish LSD from saline revealed that tryptamine derivatives exhibit a pronounced similarity to the stimulus caused by LSD. Although none of them has completely replaced, the stimulus elicited by LSD, DMT and 5-MeO-DMT replaced them at great extent (Helsley et al. 1998). 5-MeO-DIPT also showed an intermediate degree as a substitute of LSD stimulus in rats with a dose-dependent suppression of response rates (Fantegrossi et al. 2006). In turn, in rats trained to discriminate DMT (Gatch et al. 2009) and DIPT (Carbonaro et al. 2013) from saline, full substitution for the discriminative stimulus effects occurred with LSD, DOM and MDMA. In both cases, methamphetamine failed in the substitution for the discriminative stimulus, which suggests that these compounds do not share the same mechanisms of action for their discriminative stimulus effects. Thus, DMT and DIPT seem to produce predominately hallucinogenic-like discriminative stimulus with minimal psychostimulant effects (Carbonaro et al. 2013; Gatch et al. 2009). Drug discrimination studies in rats using psilocybin as the training drug showed a complete replacement for DOM, LSD and psilocin (Winter et al. 2007).

Many behavioral paradigms have been used to evaluate the effects of hallucinogens, but, in general, these studies have evidenced that almost all the characteristic effects are mediated by activation of 5-HT_{2A} receptors in brain. For example, pretreatment with ketanserin or pirenperone, two selective 5-$HT_{2A/2C}$ antagonists, blocked the stimulus effects of hallucinogens (Appel and Callahan 1989; Colpaert et al. 1982; Cunningham and Appel 1987; Glennon 1986; Glennon et al. 1983). Another study revealed that stimulus cues in animals trained with LSD (Benneyworth et al. 2005; Gresch et al. 2007; Marona-Lewicka et al. 2005; Winter et al. 2004) and psilocybin (Winter et al. 2007) can be blocked using M100907, a 5-HT_{2A} antagonist with high selectivity. By contrast, neither the selective 5-HT_{2C} antagonist SB242,084 nor the mixed 5$HT_{2C/2B}$ antagonists SB200,646A and SB200,553 blocked stimulus control induced by these drugs (Gresch et al. 2007; Schreiber et al. 1994; Smith et al. 1998, 1999; Winter et al. 2007).

Abnormal behaviors and an increased impulsiveness have also been described after consumption of tryptamine hallucinogens. Fantegrossi et al. (2006) showed that 5-MeO-DIPT, but not DMT, induces the head-twitch response in mice and that these effects were antagonized by prior administration of a selective 5-HT_{2A} antagonist, reinforcing that the 5-HT_{2A} receptor is an important site of action for 5-MeO-DIPT (Fantegrossi et al. 2006). The same behavior was observed for DPT (Fantegrossi et al. 2008a), psilocin and 5-MeO-DMT (Halberstadt et al. 2011). Head-twitch responses induced by hallucinogens such as LSD and psilocin are compromised in 5-HT_{2A} −/− knockout mice (Gonzalez-Maeso et al. 2007), thus corroborating the involvement of 5-HT_{2A} receptors to this behavior.

Additional behavioral studies revealed that DMT and 5-MeO-DMT administered intravenously cause an evident inhibition of rats fighting at higher doses but no significant effects at lower doses (Walters et al. 1978). These effects are totally the opposite of those induced by LSD that facilitates the fighting at low doses, but does not produce effects at high doses (Sheard et al. 1977). The authors argue that this differential behavior may be related to the affinity of LSD for dopamine binding sites in the brain, which in turn does not exist for DMT and 5-MeO-DMT.

Regarding the locomotor activity, tryptamines exhibit a characteristic profile. When psilocin, DMT, 5-MeO-DMT and 5-MeO-AMT are tested in rodents in a novel environment, a decreased locomotor activity and exploratory behaviors and increased avoidance of the center region are observed (Adams and Geyer 1985a; Geyer et al. 1979; Halberstadt and Geyer 2011). On the other hand, these effects are not observed when animals are tested in a familiar location, because tryptamines potentiate the neophobia (tendency of an animal to avoid an unfamiliar object or situation) and agoraphobia (a reluctance to go outside) in rodents (Halberstadt and Geyer 2011). This behavior can be explained by the fact that the stimuli associated with the test environment have become less threatening due to habituation, making the animals treated with hallucinogens

more predisposed to explore the location (Halberstadt and Geyer 2011). LSD has similar effects on exploratory behavior (Adams and Geyer 1985b), but causes a biphasic locomotor pattern with an activity initially suppressed but with tendency to increase over time (Mittman and Geyer 1991). The selective 5-HT_{1A} antagonist WAY-100635 has the ability to block this initial suppression, while LSD-induced hyperactivity is blocked by both mixed 5-$HT_{2A/C}$ antagonist ritanserin (Mittman and Geyer 1991) and the selective 5-HT_{2A} receptor antagonist M100907 (Ouagazzal et al. 2001). In turn, the behavior profile produced by AET is described as extremely similar to that of MDMA. A dose–response study showed that different doses of AET (5, 10 and 20 mg/kg) injected in rats significantly enhanced locomotor activity in a dose-dependent manner (Krebs and Geyer 1993). This hyperactive behavior is not observed with traditional hallucinogens as LSD, in an initial stage, but is in turn produced by MDMA (Callaway et al. 1990). Moreover, likewise MDMA (Callaway et al. 1990), the behavior induced by AET was attenuated by pretreatment with fluoxetine (a selective serotonin reuptake inhibitor) (Krebs and Geyer 1993), indicating that serotonin release is necessary to the locomotor effects observed with these drugs. In another study, 5-MeO-DMT administered in combination with MAO inhibitors (alike ayahuasca) produced an initial decrease in locomotor behavior in rats, followed by a LSD-like late hyperactivity that was completely blocked by the 5-HT_{2A} antagonist MDL 11,939 but unaffected by WAY-100635 (Halberstadt et al. 2008), indicating that the hyperactivity is mediated by 5-HT_{2A} receptor activation.

Additional behavioral studies also demonstrated that rats treated during adolescence with repeated doses of 5-MeO-DIPT (5 or 20 mg/kg, with a total of six injections spaced at 48-h intervals) were able in adulthood to master the spatial navigation tests similar to control rats, but, regardless of the dose, the performance of 5-MeO-DIPT-treated rats was clearly lower in certain tasks that require the use of spatial memory, suggesting a deficit of attention (Compton et al. 2011). In this study, similar to MDMA (Sabol et al. 1996; Scanzello et al. 1993), rat brain serotonin levels were reduced, suggesting that 5-MeO-DIPT may elicit its adverse behavioral effects by affecting the serotonergic systems (Compton et al. 2011). In another study, Williams et al. (2007) examined the performance of adult rats in behavioral tasks following the administration of 20 mg/kg of 5-MeO-DIPT (four times at 2-h intervals on a single day); animals showed hypoactivity and, in a test of path integration, drug-treated rats displayed deficit in performance, although no differences were detected on tests of novel objects or place recognition, suggesting that 5-MeO-DIPT only alters the rats' ability to perform certain cognitive tasks (Williams et al. 2007). However, neonatal rats treated subcutaneously with repeated doses of 5-MeO-DIPT (10 mg/kg, four times daily with 2-h intervals) showed spatial learning deficits (although less severe than those caused by MDMA at the same dose), but no deficits were observed in spatial memory or path integration (Skelton et al. 2009).

Experimental studies to evaluate the influences of tryptamine derivatives on thermoregulation were also performed. Brimblecombe (1967) assessed the behavior and the rectal temperature of rats and rabbits after subcutaneous administration of 36 tryptamine derivatives. The results showed that some compounds had no effect on the evaluated parameters, while others induced only behavioral alterations and most of them produced significant effects in both parameters. A significant correlation between the potency (minimal effective dose) of the compounds and produced effects was observed, suggesting that these derivatives share common pharmacological receptors with LSD (Brimblecombe 1967). Williams et al. (2007) monitored the rat body temperature after repeated administrations of 5-MeO-DIPT (0, 10 or 20 mg/kg, four times at 2-h intervals) on a single day. Rats exhibited hypothermia during the administration period, followed by a hyperthermic response on post-drug period (24 h after the last dose). High levels of corticosterone were also present in plasma in a dose-dependent manner with minor changes in 5-HT turnover and no changes in monoamine levels (Williams et al. 2007). Hyperthermia was also observed after administration of low doses (0.5 µg/kg) of LSD in rabbits (Horita and Dille 1954). Studies investigating the hyperthermic effects elicited by LSD suggest that the same type of excitation produced by 5-HT in CNS is responsible for the effect (Elder and Shellehberger 1962; Horita and Gogerty 1958).

Subjective effects and adverse reactions in humans

The effects caused by hallucinogens in humans are fairly subjective and hard to assess. In general, tryptamine derivatives are characterized by a relatively fast onset of their effects. The effects reported by users vary between compounds and routes of administration, but, in general, the hallucinogenic effects overrule (Alatrash et al. 2006; Boland et al. 2005; Ikeda et al. 2005; Meatherall and Sharma 2003; Smolinske et al. 2005; Wilson et al. 2005), although stimulant effects are also mentioned. These stimulant properties occur particularly for alpha-methylated tryptamines and seem to be related to the presence of the methyl group on the alpha carbon (Lessin et al. 1965), a characteristic shared with amphetaminic compounds, conferring resistance to MAO-mediated metabolism. Dose–response studies with DMT in humans showed that visual hallucinations predominate at higher doses, while

the stimulant effects are more prominent at lower doses (Strassman and Qualls 1994; Strassman et al. 1994).

Hallucinogens are capable of producing complex mental and perceptual alterations, the result of a marked alteration of consciousness (Halberstadt and Geyer 2013). Perceptual effects encompass hypersensitivity, distortions, illusions, auditory/visual/sensory hallucinations, changes in the sense of time and space, feeling of unreality and depersonalization (Alatrash et al. 2006; Boland et al. 2005; Halberstadt and Geyer 2013; Muller 2004; Wilson et al. 2005). Other neurologic and neuropsychiatric effects can include ataxia, hyperreflexia, clonus, severe agitation, psychosis, paranoia, delusions, confusion, excited delirium, echolalia, anterograde amnesia and catalepsy (Brush et al. 2004; Itokawa et al. 2007; Jovel et al. 2014; Meatherall and Sharma 2003; Shimizu et al. 2007; Smolinske et al. 2005; Taljemark and Johansson 2012). Tryptamine derivatives can induce panic reactions, commonly known as 'bad trips', and prolonged psychotic or depressive reactions are described in users with a preexisting psychopathology (Fuse-Nagase and Nishikawa 2013; Halberstadt and Geyer 2013; Ikeda et al. 2005). Tremors and seizures are rarely described (Smolinske et al. 2005). The effects caused by tryptamines depend on the personality and mood of each user, as well as on the environment in which these substances are consumed (Halberstadt and Geyer 2013). The hallucinations and altered perception may not appear immediately, with reports of panic attacks experienced days after the tryptamine consumption, sometimes months or years later, a phenomenon known as 'flashbacks' (Ikeda et al. 2005; Peden et al. 1981).

Tryptamine users exhibit vital signs abnormalities, namely tachycardia, tachypnea and hypertension, and in severe intoxications, hyperthermia may also occur (Alatrash et al. 2006; Brush et al. 2004; Jovel et al. 2014; Muller 2004; Peden et al. 1981; Smolinske et al. 2005; Taljemark and Johansson 2012). Reports of rhabdomyolysis and renal failure are also described (Alatrash et al. 2006; Jovel et al. 2014). Other clinical effects include trismus, anxiety, euphoria, sweating, diarrhea, nausea, vomiting, abdominal pain, sialorrhea, diaphoresis, palpitations, drowsiness, dysphoria and mydriasis (Boland et al. 2005; Ikeda et al. 2005; Itokawa et al. 2007; Jovel et al. 2014; Muller 2004; Peden et al. 1981; Shimizu et al. 2007; Smolinske et al. 2005; Wilson et al. 2005).

The effects of tryptamines are also characterized by their short duration in humans, which could lead to a repeated and continued consumption resulting in an elevated risk of subsequent tryptamine dependence. However, according to the recent survey developed by Winstock et al. (2014), DMT consumption does not seem to translate into a greater boost to consumption. Gable (2007) states that there is no evidence of dependence potential of oral administered DMT. Dose–response studies in hallucinogen users carried out by Strassman et al. (1996) demonstrate that DMT administered intravenously does not cause tolerance regarding psychological effects. However, cardiovascular and neuroendocrine effects reduced with repeated doses, suggesting the development of tolerance regulated by a distinct mechanism (Strassman et al. 1996). Data on the symptoms associated with withdrawal of tryptamines were not found in the literature.

Hallucinogens are powerful drugs able to produce altered states of consciousness at doses that are considered harmless to organ systems. According to Nichols (2004), the tryptamine compounds are unlikely to cause life-threatening changes in cardiovascular, renal or hepatic function because of their little or no affinity for relevant biological receptors and targets; nevertheless, despite having been reported safe drugs, the consumption of synthetic tryptamines has been associated with fatal cases in recent years (Boland et al. 2005; Corkery et al. 2012; Tanaka et al. 2006). The ingestion of 5-MeO-DIPT ('foxy') resulted in one death in Japan (Tanaka et al. 2006). The individual (male, 29 years) applied the substance rectally in order to improve his sexual experience. He was taken to the hospital with a very intense agitation and died 3 h later. The autopsy revealed evidence of myocardial ischemia, advanced pulmonary congestion and pulmonary alveolar hemorrhage. Toxicological analyses carried out in postmortem fluids (blood and urine) by LC–MS identified the 5-MeO-DIPT and its two metabolites, 5-OH-DIPT and 5-MeO-NIPT. The levels of 5-MeO-DIPT, 5-OH-DIPT and 5-MeO-NIPT in blood and urine samples were 0.412, 0.327 and 0.020 μg/ml, and 1.67, 27.0 and 0.32 μg/ml, respectively, at concentrations higher than those published in other cases of 'foxy' intoxications (Meatherall and Sharma 2003; Vorce and Sklerov 2004; Wilson et al. 2005). Therefore, the cause of death was considered to be acute cardiac failure due to 'foxy' overdose.

The concomitant exposure to tryptamines and MAO inhibitors can have serious consequences. Besides prolonging the tryptamines effects by attenuating MAO-mediated oxidative deamination, both MAO inhibitors and tryptamines act agonistically on central 5-HT receptors (serotonergic systems) causing hyperserotonergic effects or serotonin toxicity. In fact, it has been reported that ingestion of high dose of 5-MeO-DMT in combination with a MAO inhibitor resulted in a fatality (Sklerov et al. 2005).

AMT also appears associated with a fatal case reported in the USA (Boland et al. 2005). The case involved a young student (male, 22 years) who consumed AMT (an empty 1-g vial of AMT was recovered from the scene; the route of administration was unknown) and developed severe agitation and visual hallucinations; 12 h later, he was discovered unresponsive. Toxicological analyses performed in blood,

gastric content, liver and brain tissues revealed the following AMT concentrations: 2.0 mg/L, 9.6 mg, 24.7 mg/kg and 7.8 mg/kg, respectively. Further data on AMT concentration in postmortem specimens or tissue distribution are unknown.

Moreover, the hallucinogenic effects of tryptamines can alter the perception and cause behavioral disorders that may result in life-threatening situations (Corkery et al. 2012). Corkery et al. (2012) report a fatal case associated with the consumption of 5-MeO-DALT. A young male snorted 350 mg of 5-MeO-DALT purchased via the Internet (14 times higher than the typical maximum dose reported). After consumption, he was seen to walk out into the slow lane of a motorway, putting him in front of a heavy goods vehicle, possibly as a result of its hallucinogenic state.

There is no specific antidote for the treatment of tryptamines intoxication, and the treatment may be similar to other sympathomimetic agonists and consists of supportive therapy targeted specifically to the symptoms observed (Itokawa et al. 2007; Jovel et al. 2014; Muller 2004; Nelson et al. 2014; Shimizu et al. 2007; Smolinske et al. 2005; Wilson et al. 2005). The priority is to correct the patient's vital signs with a combination of supportive care and sedation. Activated charcoal may be useful after oral exposure but has limited efficacy when the drugs have been insufflated or smoked. Benzodiazepines can be used to treat agitation, hypertension and hallucinations, and vital signs severely disturbed may require treatment with β-adrenergic antagonists or nitroprusside (Arunotayanun and Gibbons 2012; Babu et al. 2005; Brush et al. 2004).

Concluding remarks

The search for recreational drugs with hallucinogenic properties has been rising at an alarming rate. Among these drugs, tryptamines require especial attention due to their high affinity and effectiveness for the serotonin 5-HT_{2A} receptor, the main responsible for mediating the effects of hallucinogens in human subjects as well as in animal behavioral paradigms. Natural tryptamines have been used by mankind for millennia, but new tryptamine derivatives have been replacing the consumption of traditional hallucinogens, not only for their strong activity, but also due to legal voids that frequently permit their decriminalized trade. Available information on these new tryptamine derivatives is very scarce, namely concerning their acute and long-term effects, their possible interactions with other substances, their toxicological risks or even their addictive potential. Although hallucinogens are generally considered to be physiologically safe molecules, reports of intoxication and deaths related to the use of recreational tryptamines have been described over the last years. Therefore, more research on their pharmacological and toxicological properties is fully required in order to access the actual potential hazard of synthetic tryptamines. The present manuscript intends to contribute for a better knowledge of these drugs by providing a comprehensive update on these drugs, concerning their evolution, prevalence, patterns of use and legal status, chemistry, toxicokinetics, toxicodynamics and their physiological and toxicological effects on animals and humans. After completing the task, the take home message is that much is still to be researched on hallucinogenic tryptamines but also that, from what is already known, the searched hedonistic trips frequently represent a jump to the abysm of permanent disease and death.

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