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REVIEW ARTICLE

Metabolism and toxicological analyses of hallucinogenic tryptamine analogues being abused in Japan

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Abstract Hallucinogenic tryptamine analogues, an important class of drugs of abuse, can be naturally occurring or chemically synthesized compounds. In Japan, psilocin and psilocybin (ingredients of "magic mushrooms") and 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT; a synthetic tryptamine) seem to be particularly problematic due to their extensive abuse. This review is focused on human metabolism and forensic toxicological analyses of the above three tryptamine analogues. In humans, psilocybin is rapidly dephosphorylated to form psilocin, and most of the psilocin is eventually conjugated to form its glucuronide. On the other hand, 5-MeO-DIPT is mainly metabolized via *O*-demethylation, 6-hydroxylation, and *N*-deisopropylation, partly followed by conjugation to form their sulfates and glucuronides. Suitable hydrolysis should be, therefore, applied for sensitive and effective analysis of the metabolites. In analyzing psilocin and psilocybin by gas chromatography-mass spectrometry (GC-MS), derivatization is necessary for their discriminative identification. Although 5-MeO-DIPT and its three major metabolites can be analyzed by GC-MS without any derivatization, trimethylsilyl derivatization provides improvement of their peak shapes and intensities. In contrast to GC-MS, liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry allow us not only to discriminate psilocin and psilocybin without derivatization, but also to directly analyze their conjugated metabolites.

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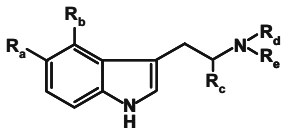
Introduction

Hallucinogenic tryptamine (indole) analogues, which belong to an important class of drugs for abuse, together with phenethylamine and piperazine derivatives are causing social problems throughout the world. Such tryptamine analogues have structural similarities to the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT), and their hallucinogenic effects are thought to appear through 5-HT receptors [1]. Some of these compounds occur as natural ingredients, but most of them are chemically synthesized as designer drugs.

As naturally occurring hallucinogenic tryptamine analogues, *N,N*-dimethyltryptamine (DMT), psilocin, and psilocybin are well known. DMT is a hallucinogenic ingredient of "Ayahuasca," an Amazonian religious tea, and psilocin and psilocybin occur in "magic mushrooms," such as *Psilocybe mexicana*, *Psilocybe cubensis*, and *Psilocybe argentipes*, which were originally used in religious ceremonies in Mesoamerica [2]. Nowadays, magic mushrooms are used extensively as recreational hallucinogenic substances in various countries, causing intoxication due to overdoses. In Japan, such mushrooms are now controlled by the Narcotics and Psychotropics Control Law since 2002, and their possession, cultivation, and intake are totally prohibited. Such a measure prevented further popularity of magic mushrooms to some extent, but their cultivation and possession still occur.

Fig. 1 Nineteen tryptamine analogues controlled or regulated by Japanese laws



	R_a	R_b	R_c	R_d	R_e
Narcotic					
Etryptamine	H	H	CH_2CH_3	H	H
α-Methyltryptamine (AMT)	H	H	CH_3	H	H
5-Methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT)	OCH_3	H	H	$CH(CH_3)_2$	$CH(CH_3)_2$
Diethyltryptamine (DET)	H	H	H	CH_2CH_3	CH_2CH_3
Dimethyltryptamine (DMT)	H	H	H	CH_3	CH_3
Psilocin	H	OH	H	CH_3	CH_3
Psilocybin	H	OPO_3H_2	H	CH_3	CH_3
Designated substance					
4-Acetoxy-*N,N*-diisopropyltryptamine (4-AcO-DIPT)	H	$OCOCH_3$	H	$CH(CH_3)_2$	$CH(CH_3)_2$
N-Methyl-*N*-isopropyl-tryptamine (MIPT)	H	H	H	CH_3	$CH(CH_3)_2$
5-Methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MIPT)	OCH_3	H	H	CH_3	$CH(CH_3)_2$
5-Methoxy-*N*-ethyl-*N*-isopropyltryptamine (5-MeO-EIPT)	OCH_3	H	H	CH_2CH_3	$CH(CH_3)_2$
5-Methoxy-*N,N*-diallyltryptamine (5-MeO-DALT)	OCH_3	H	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$
N,N-Diisopropyltryptamine (DIPT)	H	H	H	$CH(CH_3)_2$	$CH(CH_3)_2$
5-Methoxy-*N,N*-diethyltryptamine (5-MeO-DET)	OCH_3	H	H	CH_2CH_3	CH_2CH_3
N,N-Dipropyltryptamine (DPT)	H	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
4-Hydroxy-*N,N*-diisopropyltryptamine (4-OH-DIPT)	H	OH	H	$CH(CH_3)_2$	$CH(CH_3)_2$
5-Methoxy-α-methyltryptamine (5-MeO-AMT)	OCH_3	H	CH_3	H	H
5-Methoxy-*N,N*-dipropyltryptamine (5-MeO-DPT)	OCH_3	H	H	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT)	OCH_3	H	H	CH_3	CH_3

Various kinds of tryptamine analogues have been chemically synthesized from DMT by modifying its structure, and have been recently introduced into the black market as hallucinogenic drugs. The modifications were performed mainly at the 4- or 5-position of the indole ring and/or on the amino moiety. Among the derivatives of tryptamine, 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT) [3] is one of the most prominent tryptamine analogues for its popularity and toxicity; there was much concern about its widespread distribution, and it was prohibited in 2005 in Japan. However, its abuse has never been reduced. The appearance of newly synthesized tryptamine derivatives as hallucinogenic drugs and countermeasure control by the drug enforcement authorities continue to occur. Now in Japan, 7 tryptamine analogues are being controlled as narcotics, and 12 (tryptamines) are being regulated as "designated substances" (Fig. 1) for import, synthesis, and sale. In addition, some herbal products containing indole compounds exhibiting psychotropic

activities have been reported in Japan [4,5]; they are neither controlled nor regulated because their pharmaceutical effects have not been scientifically proven, and they are sold over the Internet.

The identification of a drug type used is an important task for forensic toxicologists. To disclose drugs of abuse in human specimens, detection of the drugs themselves and/or their metabolites that retain the structural characteristics of the precursor drugs is usually performed. The elucidation of the metabolic pathways of new drugs, the choice of the appropriate analytical targets, and methods that allow us to achieve sensitive and reliable identification are absolutely necessary. However, few studies of the metabolism of hallucinogenic tryptamine analogues in humans have emerged. Therefore, we studied the metabolism and the analytical procedures using gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and liquid chromatography-tandem mass spectrometry (LC-MS-MS) [6–9].

This review describes human metabolism and forensic toxicological analyses of psilocin, psilocybin, and 5-MeO-DIPT, the abuse of which are widespread in Japan.

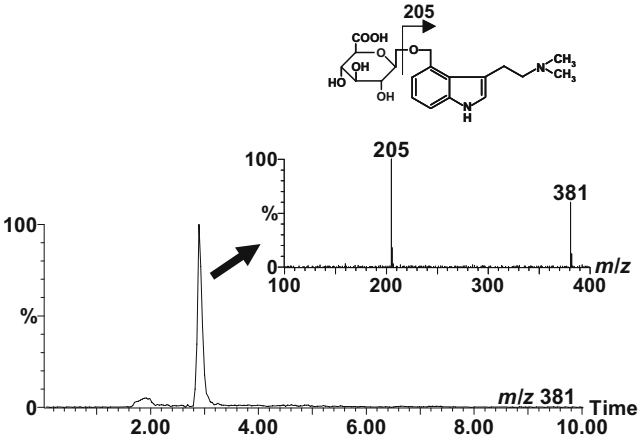


Fig. 2 Mass chromatogram at *m/z* 381 obtained from urine of a "magic mushroom" abuser without hydrolysis and a product ion spectrum obtained from the precursor ion at *m/z* 381 appearing at 2.9 min [4]

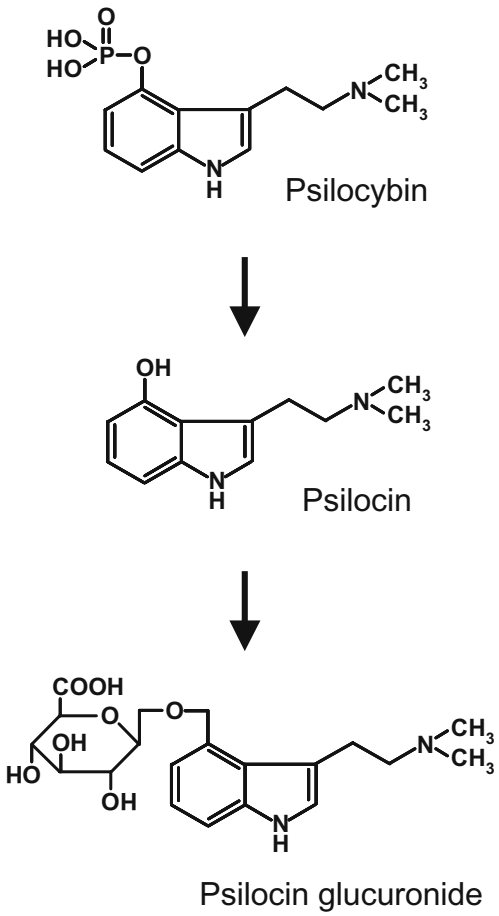


Fig. 3 Metabolic pathway of psilocin and psilocybin in humans [4]

Metabolism in humans

Psilocin and psilocybin

Magic mushrooms generally contain both psilocin and its phosphate psilocybin, and some reports have been published on the metabolism of both psilocybin and psilocin in humans based on specimens from abusers. In 1961 and 1962, psilocybin was reported to be rapidly dephosphorylated to form psilocin by phosphatase in human bodies [10,11]. Sticht and Käferstein [12] and Grieshaber et al. [13] reported the analysis of psilocin in serum and urine specimens from magic mushroom abusers. Administration experiments also showed the conversion of psilocybin into psilocin in healthy volunteers [14–16]. The psilocin concentrations in biological samples were also reported to increase via enzymatic hydrolysis with β-glucuronidase [12,13,15], suggesting that psilocin is subject to conjugation in the glucuronide form. We recently demonstrated the conjugation pathway (Figs. 2 and 3) by direct detection of psilocin glucuronide from urine and serum samples of a magic mushroom abuser using LC-MS and LC-MS-MS [6,7]; other conjugates of psilocin such as sulfate, methyl, and glucose conjugates were not detected in urine samples [6].

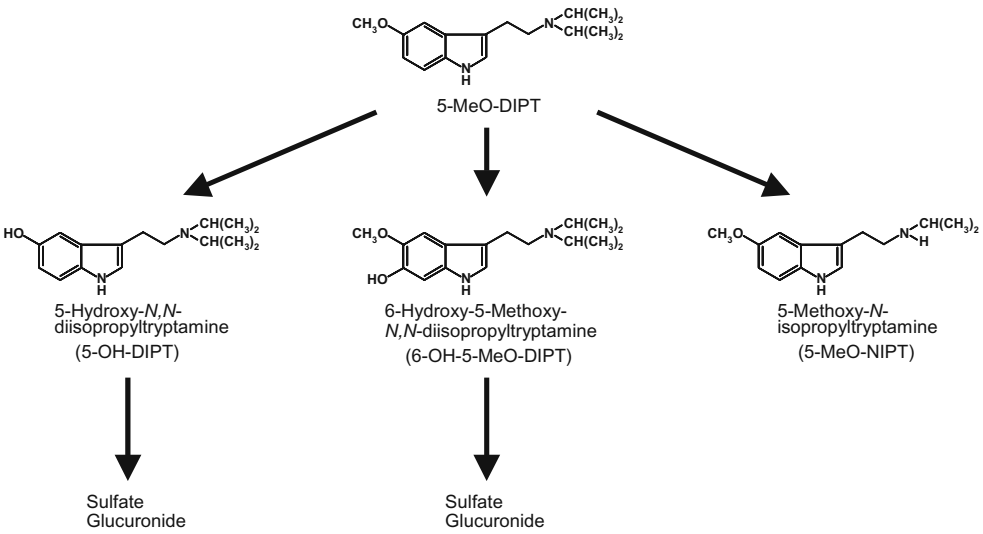


Fig. 4 Metabolic pathways of 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT) in humans [6]

5-Methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT)

On the metabolism of 5-MeO-DIPT, Meatherall and Sharma [17] reported the excretion of *N*-deisopropylated and *N*′-oxide metabolites in urine of 5-MeO-DIPT abusers. Wilson et al. [18] detected an *O*-demethylated metabolite of 5-MeO-DIPT, along with the previously reported metabolites, in urine of 5-MeO-DIPT abusers. However, both reports gave tentative identification of the metabolites without any authentic standard. We synthesized the expected metabolites of 5-MeO-DIPT, and unequivocally confirmed them by analyzing urine collected from 5-MeO-DIPT abusers using GC-MS and LC-MS techniques as follows. Three important metabolic pathways for 5-MeO-DIPT to produce three metabolites, which retained structural characteristics of the precursor compound, were found to exist in humans (Fig. 4) [8]. The first pathway leads, via side-chain *O*-demethylation, to 5-hydroxy-*N,N*-diisopropyltryptamine (5-OH-DIPT), partly followed by conjugation to form its sulfate and glucuronide. The second pathway leads, via hydroxylation at position 6 of the aromatic ring, to 6-hydroxy-5-methoxy-*N,N*-diisopropyltryptamine (6-OH-5-MeO-DIPT), mainly followed by conjugation to form its sulfate and glucuronide. The third pathway leads, via side-chain *N*-dealkylation, to the corresponding secondary amine, 5-methoxy-*N*-isopropyltryptamine (5-MeO-NIPT). Of these characteristic metabolites, both 5-OH-DIPT and 6-OH-5-MeO-DIPT were expected to be the most abundant. In addition, it was demonstrated that 5-MeO-DIPT-*N*-oxide was not detectable in human urine [8]. Among these metabolisms, the *O*-demethylation and the deisopropylation were reported to be catalyzed by CYP2D6 and by CYP1A2, CYP2C8, and CYP3A4 in human liver, respectively, by Narimatsu et al. [19]. Metabolic pathways similar to those for 5-MeO-DIPT were recently demonstrated for another tryptamine-derived hallucinogen 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MIPT) by Shima et al. [20]; not only 5-hydroxy-*N*-methyl-*N*-isopropyltryptamine and 6-hydroxy-5-methoxy-*N*-methyl-*N*-isopropyltryptamine were detected, but also their glucuronides and sulfates. However, it is of great interest that only the *N*-demethylation product 5-MeO-NIPT was detected by *N*-dealkylation; *N*-deisopropylation did not take place. This is probably due to the steric hindrance of the longer isopropyl group. More recently, on the other hand, we found in rat specimens that the corresponding *N*-oxides were predominantly excreted into urine after oral administration of 5-methoxy-*N,N*-dimethyltryptamine or 5-methoxy-*N,N*-diethyltryptamine [21]. From these data, it is assumed that for the 5-methoxy-*N,N*-dialkyltryptamines, the metabolic pathways to *N*-oxide or 6-hydroxy metabolites are chosen according to the bulkiness of the alkyl groups bound to the amino groups. However, more studies are needed to clarify the correlation between chemical structures and metabolic pathways for 5-methoxy-*N,N*-dialkyltryptamines, taking the species differences into consideration.

Forensic toxicological analyses

Sample preparation for body fluids

To efficiently detect drug metabolites in body fluids with adequate sensitivity, sample pretreatments are essential

in toxicological analyses. In urine samples that contains a number of conjugated metabolites, hydrolysis sometimes gives good results, because the most of the conjugated standards are not available, and so the analytical targets are generally not conjugates themselves but free forms liberated from them. As mentioned for psilocin, psilocybin, and 5-MeO-DIPT in the above section, their major urinary metabolites that contain hydroxyl moieties in their structures are certainly excreted as conjugates in humans. The hydrolysis of the conjugated metabolites seems indispensable for forensic urine analysis. In the hydrolysis methods previously published [13,15], the increase in free form levels after hydrolysis was only monitored, and it was not clarified whether the conjugates were completely cleaved. Thus, we tried to directly analyze the conjugates by LC-MS, and optimized the hydrolysis conditions by confirming the decrease in the conjugates.

For psilocin glucuronide in urine, acid hydrolysis techniques and four kinds of β-glucuronidases from different origins were examined, and the *Escherichia coli* enzyme was found to provide the best results [6]. The urinary psilocin glucuronide was completely hydrolyzed by 5000 units/ml urine of *E. coli* β-glucuronidase under incubation at pH 6 and 37°C for 2 h. The *E. coli* β-glucuronidase also gave complete hydrolysis of serum psilocin glucuronide at 3000 units/ml serum when ascorbic acid (10 μmol/ml serum) was added to prevent decomposition of liberated psilocin [7]. On the other hand, *Helix pomatia* sulfatase/β-glucuronidase efficiently hydrolyzed both sulfate and glucuronide metabolites of 5-MeO-DIPT in urine [8,9]. Incubation at pH 5 and 45°C for 3 h with 3000 units/ml urine of sulfatase (with 86 800 units/ml urine of β-glucuronidase) was proposed. The addition of ascorbic acid (30 μmol/ml urine) was also required to suppress the decomposition of labile 6-OH-5-MeO-DIPT during the hydrolysis, because the hydrolysis under weakly acidic conditions caused significant decrease in 6-OH-5-MeO-DIPT. The urine and serum specimens after the enzymatic hydrolysis were used directly in liquid–liquid extraction and solid-phase extraction without further time-consuming pretreatments.

GC-MS and LC-MS(-MS)

In forensic toxicology, mass spectrometry is the most reliable technique to identify drugs and/or their metabolites in extracts containing a number of unknown biological matrix elements. In particular, capillary GC-MS is the most widely used technique for unequivocal identification of unknown compounds due to its high sensitivity, specificity, and the availability of electron ionization (EI) mass spectral libraries. It also provides separation of analytes in complex mixtures including biological impurities as a result of the high number of theoretical plates.

For toxicological analyses of psilocin and psilocybin, it is often necessary to separately determine both compounds in mushrooms or stomach contents. However, psilocybin is rapidly degraded to form psilocin at high temperature [22], and is thus detected as psilocin by GC-MS. Therefore, use of GC-MS requires derivatization before analysis for discriminative identification of psilocybin and psilocin. For efficient derivatization, trimethylsilylation with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) was successful for both psilocin and psilocybin in mushrooms [23] and body fluids [12,13].

For 5-MeO-DIPT and its metabolites in body fluids, Meatherall and Sharma [17] and Wilson et al. [18] reported the use of GC-MS without derivatization using nonpolar and weakly polar columns, respectively. GC-MS with pentafluoropropionyl derivatization of 5-MeO-DIPT was also reported by Vorce and Sklerov [24]. More recently, we identified 5-MeO-DIPT and its three major metabolites by GC-MS using a weakly polar column with and without derivatization [9]; the trimethylsilyl derivatization with MSTFA resulted in improved peak shapes and intensities.

LC-MS(-MS) is more useful than GC-MS for analysis of thermolabile, nonvolatile, and highly polar compounds such as drug metabolites, although less mass spectral information for identification can be obtained. We successfully discriminated psilocybin from psilocin in magic mushrooms without derivatization by LC-MS (-MS) with positive electrospray ionization (ESI) mode [25]. In this study, complete chromatographic separation of psilocybin and psilocin was achieved with a widely used octadecylsilyl (ODS) column using an acidic mobile phase to suppress dissociation of the phosphoric acid moiety of psilocybin. We also developed an analytical method to simultaneously detect psilocin and its glucuronide in abuser urine and serum by LC-MS-MS using an ODS column and a gradient mobile phase system. This method was applied to optimization of the enzymatic hydrolysis conditions [6,7].

For 5-MeO-DIPT in blood and urine, Vorce and Sklerov [24] reported the use of LC-ESI-MS using a phenyl-hexyl column for screening and confirmation. Recently, we reported the simultaneous determination of 5-MeO-DIPT and its three metabolites in human urine by LC-ESI-MS with an ODS column using a gradient mobile phase system, and we applied the method to abuser urine specimens [8] (Fig. 5). Direct analysis of the conjugates of the main metabolites was also described.

Table 1 Psilocin concentrations in human serum and urine specimens in intoxication cases

Specimen	Concentrations (μg/ml)		Reference
	Total	Free	
Serum	0.052	0.018	[12]
Urine	1.76	0.23	[12]
Urine	0.030	<LOQ	[13]
Urine	0.060	0.041	[13]
Urine	0.058	<LOQ	[13]
Urine	>0.200	<LOQ	[13]
Urine	0.046	<LOQ	[13]
Urine	0.044	<LOQ	[13]
Urine	3.6	nd	[6]

LOQ, limit of quantitation; nd, not detected

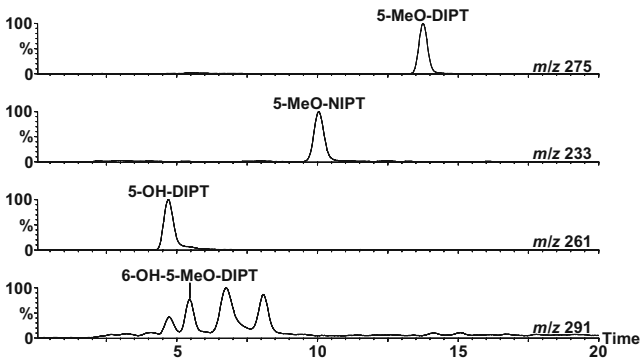


Fig. 5 Liquid chromatography-mass spectrometry mass chromatograms obtained from urine of a 5-MeO-DIPT abuser [6]. *NIPT*, *N*-isopropyltryptamine

Analysis of tryptamine analogue drugs of abuse in human body fluids in actual cases

Psilocin and psilocybin are found in magic mushrooms in a wide range of levels [25], and this is probably the reason that reported values of psilocin levels in human serum and urine obtained from intoxicated cases exhibit great variance as shown in Table 1. We tried to determine psilocin in a urine specimen collected from a magic mushroom user 8 h after intake with and without the enzymatic hydrolysis; free psilocin was not detected without hydrolysis [6]. Therefore, we further quantitated total and free psilocin levels in serum specimens collected at various intervals from the abuser [7] (Table 2). The hydrolysis significantly increased the psilocin levels, indicating that a considerable portion of psilocin is in the conjugated form even in blood, and that the hydrolysis enabled longer detectable periods for psilocin in serum specimens.

Cases of 5-MeO-DIPT intoxication have been often reported since the early 2000s, and the concentrations of unchanged 5-MeO-DIPT in human body fluids were reported by Meatherall and Sharma [17], Vorce and Sklerov [24], and Wilson et al. [18] (Table 3). Recently, we also described the concentrations of 5-MeO-DIPT and its major metabolites, 5-OH-DIPT, 6-OH-5-MeO-DIPT, and 5-MeO-NIPT, in 11 specimens from 6 abusers of 5-MeO-DIPT [9] (Table 3). The data showed that enzymatic hydrolysis dramatically increased the 6-OH-5-MeO-DIPT concentrations to levels similar to those of 5-OH-DIPT, and that the detectable periods in urine were much longer for the metabolites (longest period of 80 h for 5-OH-DIPT and 60 h for 6-OH-5-MeO-DIPT and 5-MeO-NIPT) than for the precursor drug (longest period of 35 h) (Table 3). These findings demonstrate that urinary 5-OH-DIPT and 6-OH-5-MeO-DIPT are good indicators for the intake of 5-MeO-DIPT. Also, as shown in Table 3, Tanaka et al. [26] reported a peculiar fatal case, in which a man intrarectally used 5-MeO-DIPT and died about 3.5 h after the intake. The cause of his death was judged to be acute cardiac failure due to an overdose of 5-MeO-DIPT on the basis of the toxicological and autopsy findings.

Table 2 Concentrations of total and free psilocin in human serum specimens as a function of time after magic mushroom ingestion

Time after intake (h)	Concentrations (ng/ml)	
	Total	Free
5	71	13
12	58	7.2
27	14	0.83
36	4.1	nd
52	2.2	nd

Data from Kamata et al. [7]

Very recently, Shima et al. [20] reported the levels of 5-MeO-MIPT, an analogue of 5-MeO-DIPT, and its major metabolites in intoxication cases (Table 4). The data demonstrated that the metabolic pathways previously proposed for 5-MeO-DIPT are also true for 5-MeO-MIPT.

Conclusions

We have reviewed the metabolisms and forensic toxicological analyses of tryptamine-derived drugs of abuse by focusing on psilocin, psilocybin, and 5-MeO-DIPT. The findings presented here will be of great importance in the studies on the metabolisms of other psychoactive tryptamine analogue drugs of abuse, and will provide useful information for the forensic toxicological analyses even for unknown tryptamine analogues, which will be encountered in the future.

Table 3 Concentrations of 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT) and its metabolites in human serum and urine specimens

	Time after intake (h)	Concentrations (μg/ml)				Reference
		5-MeO-DIPT	5-OH-DIPT	6-OH-5-MeO-DIPT	5-MeO-NIPT	
Intoxication cases						
Urine	4	1.7	—[a]	—	—	[17]
Urine	Unknown	0.229	—	—	—	[24]
Serum	4	0.14	nd	—	nd	[18]
Urine	4	1.6	1.6[b]	—	0.1[b]	[18]
Urine	11	1.7	47 (32)	69 (2.6)	1.7	[9]
Urine	35	Trace	0.73 (0.71)	0.52 (trace[c])	0.03	[9]
Urine	80	nd	0.01 (0.01)	nd (nd)	nd	[9]
Urine	18	0.03	2.7 (2.4)	3.9 (nd)	0.45	[9]
Urine	45	nd	0.04 (0.04)	nd (nd)	Trace	[9]
Urine	12	0.54	28 (20)	11 (0.52)	1.3	[9]
Urine	60	nd	0.05 (0.05)	Trace (nd)	Trace	[9]
Urine	12	1.2	38 (20)	3.8 (0.26)	0.31	[9]
Urine	60	nd	0.03 (0.03)	nd (nd)	Trace	[9]
Urine	10	0.85	34 (22)	5.9 (0.30)	3.5	[9]
Urine	60	Trace	5.5 (4.2)	0.16 (nd)	0.04	[9]
Fatal case						
Serum	3.5	0.412	0.327	0.020	—	[26]
Urine	3.5	1.67	27.0	0.32	—	[26]

Values in parentheses for 5-OH-DIPT and 6-OH-5-MeO-DIPT represent concentrations before hydrolysis
NIPT, *N*-isopropyltryptamine
[a] Not determined
[b] Semiquantitative value
[c] Trace: <0.01 for 5-MeO-DIPT and 5-MeO-NIPT; <0.1 for 6-OH-5-MeO-DIPT

Table 4 Concentrations of 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MIPT) and its metabolites in human urine and blood specimens measured by our group

	Time after intake (h)	Concentrations (μg/ml)			
		5-MeO-MIPT	5-OH-MIPT	6-OH-5-MeO-MIPT	5-MeO-NIPT
Intoxication case					
Urine	15	0.06	7.7 (2.16)	16 (0.01)	0.24
Fatal case (death due to fall)					
Blood	4	0.18	0.02 (trace)	0.18 (nd)	0.01

Data from Shima et al. [20]. Values in parentheses for 5-OH-MIPT and 6-OH-5-MeO-MIPT represent the concentrations before hydrolysis
Trace: <0.01

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