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Metabolism and urinary disposition of *N,N*-dimethyltryptamine after oral and smoked administration: a comparative study

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***N,N*-dimethyltryptamine (DMT) is a widely distributed plant alkaloid that displays partial agonist activity at the 5-HT_{2A} receptor and induces intense psychedelic effects in humans when administered parenterally. However, self-administration studies have reported a total lack of activity following oral intake. This is thought to be due to extensive degradation by monoamine oxidase (MAO). Despite increased use of DMT and DMT-containing preparations, such as the plant tea ayahuasca, the biotransformation of DMT in humans when administered alone is relatively unknown. Here we used high performance liquid chromatography (HPLC)/electrospray ionization (ESI)/selected reaction monitoring (SRM)/tandem mass spectrometry (MS/MS) to characterize the metabolism and disposition of oral and smoked DMT. Twenty-four-hour urine samples were obtained from 6 DMT users before and after intake of 25 mg DMT doses on two separate sessions. In one session, DMT was taken orally and in another it was smoked. After oral ingestion, no psychotropic effects were experienced and no DMT was recovered in urine. MAO-dependent indole-3-acetic acid (IAA) represented 97% of the recovered compounds, whereas DMT-*N*-oxide (DMT-NO) accounted for only 3%. When the smoked route was used, the drug was fully psychoactive, unmetabolized DMT and DMT-NO rose to 10% and 28%, respectively, and IAA levels dropped to 63%. An inverse correlation was found between the IAA/DMT-NO ratio and subjective effects scores. These findings show that in the smoked route a shift from the highly efficient MAO-dependent to the less efficient CYP-dependent metabolism takes place. This shift leads to psychoactivity and is analogous to that observed in ayahuasca preparations combining DMT with MAO inhibitors. Copyright © 2014 John Wiley & Sons, Ltd.**

Keywords: DMT; metabolism; urinary excretion; human

Introduction

DMT is a potent visionary compound or psychedelic present together with 5-MeO-DMT and bufotenin in various plants of the *Anandenanthera* and *Virola* genera used historically in the preparation of the *yopo* and *epena* psychotropic snuffs in the Amazon and Orinoco river basins.[1] It is also present in the leaves of *Psychotria viridis* and *Diplopterys cabrerana*, widely used as admixtures in the preparation of the psychoactive beverage *ayahuasca*.[2,3] Interestingly, DMT has also been detected in the pineal gland of rodents[4] and there is strong evidence of its presence in human biological fluids,[5] although its physiological or physiopathological role is still unknown.

When administered parenteraly, DMT induces very potent short-acting psychedelic effects,[6,7] and like other classical psychedelics, DMT displays agonist activity at 5-HT_{2A} receptor sites.[8] However, in contrast with other compounds causing analogous effects, DMT is not psychoactive following oral administration, a peculiarity previously reported in earlier studies.[9] This lack of psychoactivity has been attributed to an intense first-pass effect involving degradation by monoamine oxidase (MAO). In effect, the main metabolite found in the urine of volunteers injected with DMT is indole-3-acetic acid (IAA), the oxidative deamination product of the parent compound.[6]

Additional support for the biotransformation of DMT by MAO is provided by the pharmacology of ayahuasca. This remarkable psychoactive tea is obtained by co-infusing the leaves of the DMT-rich *P. viridis* or *D. cabrerana* with the bark of the malpighiaceous vine *Banisteriopsis caapi*. *B. caapi* is the major source of high concentrations of the β-carboline alkaloids harmine, harmaline and tetrahydroharmine in the tea, all of which are reversible inhibitors of the MAO-A isoenzyme.[10,11] The blockade of visceral MAO brought about by the *β*-carbolines is believed to underlie the oral psychoactivity of ayahuasca.[12,13]

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Despite the growing popularity of DMT as a recreational drug[14] and of ayahuasca as a ritual sacrament,[15] the human pharmacokinetics of DMT, and specifically its metabolic fate, when administered alone has received very little attention. Oxidative deamination by MAO is not the sole metabolic pathway, as animal studies have described *N*-oxidation, *N*-demethylation and cyclization as alternative biotransformation routes.[16–18] In a recent study, DMT-*N*-oxide (DMT-NO) was found to be excreted in significant concentrations in the urine of healthy volunteers following ayahuasca intake.[19] These results show that alternative metabolic routes are available in humans even when MAO is inhibited. The chemical structure of DMT and of its two main metabolites, IAA and DMT-NO are shown in Figure 1.

Here we conducted a study comparing the metabolism and disposition of DMT in a sample of recreational users. Urine samples were obtained after intake via two different administration routes: oral ingestion, expected to display the most intense first-pass effect, and smoked intake, where first-pass effects were expected to be lower.

Materials and methods

Volunteers

The researchers contacted six recreational users of DMT (3 male and 3 female) who agreed to provide urine samples following intake of oral and smoked DMT doses. Participants had extensive experience with psychedelics and with DMT in particular. Prior to study participation they had taken the drug an average of 87 times (range: 30–170). Volunteer mean age was 32 years (range 29–41), and mean weight was 66 kg (range 46–87). Their level of education was high, all having at least a university degree; and they were employed at the moment of participation. Volunteers stated they were free of physical or psychiatric illness and not addicted to any drug. They indicated that their involvement with psychedelics reflected an intellectual interest into modified states of awareness, and regarded themselves recreational users or 'psychonauts'.

The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans, and was approved by the Sant Pau Hospital's ethics committee. All volunteers gave their written informed consent to participate.

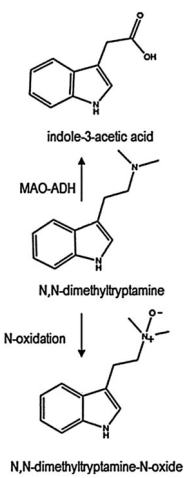

Figure 1. Chemical structures of DMT, IAA and DMT-NO and metabolic routes leading to each metabolite. MAO = monoamine oxidase, ADH = aldehyde dehydrogenase.

Drugs

Participants self-administered (orally and smoked) doses of 30 mg DMT which had been obtained by extraction from the root bark of *Mimosa tenuiflora*. According to the participants, DMT had been extracted using published methods that involved soaking the ground bark in water and lye, extracting the free base with naphtha and recrystalizing the extract. The 30 mg dose was the normal amount they usually used when smoking DMT. Subsequent analysis of a sample showed a purity of 84.6%. Thus, the actual dose taken on each session was 25.4 mg. Additional components were identified as DMT-NO (1.4%), various fatty acids and hydrocarbons of moderate molecular weights (8.2%). The remaining 6% of its composition was unidentified.

Study design and sample collection

The study involved sample collection in two separate sessions. In one of the sessions participants self-administered the DMT dose by smoking it in a water pipe. This was a bong-style pipe with heat being applied directly to the glass container where the DMT sample had been deposited. In another session, the same amount of DMT was orally ingested in a capsule. The two sessions were a week apart. It is worth noting that equivalence of dose by the two routes is affected by different factors; in the case of smoking by several factors such as pyrolysis, absorption, incomplete inhalation and exhalation among others. The oral route is mainly affected by absorption and metabolism.

Twenty-four-hour urine was collected prior to drug intake and after dosing in each of the two sessions (smoked and oral DMT, respectively). The collected urine volumes were noted and 10 ml aliquots were separated and stored at -80 ºC until analysis. In each session subjective effects questionnaires (see below) were administered 1 h after drug intake.

Analytical method

Samples were analyzed for DMT and its potential biotransformation products IAA and DMT-NO. Additionally, samples collected during the 24 h prior to each drug were also quantified for IAA which is known to be excreted under normal physiological conditions.

Urine sample analyses were conducted using a validated high performance liquid chromatography (HPLC)/electrospray ionization (ESI)/tandem mass spectrometry (MS/MS) method, as described by McIlhenny *et al.*[20] The LC-MS/MS method had been validated for the determination of DMT, IAA, and DMT-NO, among other indolealkylamine compounds. The method used 100 μL of well-mixed urine which was diluted to a volume of 1.0 mL (900 μL of LC mobile phase; 97:3 water with 0.1% formic acid:acetonitrile with 0.1% formic acid) and filtered.[20] A volume of 10 μL was injected for the analysis.

The analyses were conducted using an Agilent 1200 series LC system (Agilent Technologies, Palo Alto, CA, USA) equipped with an Agilent G1367A HiP ALS autosampler, an Agilent G1311A Quaternary micropump, and an Agilent G1332A degasser. An Agilent G131gA TCC column oven operating at 25° C was interfaced to a TSQ Quantum Access 1.5 SP1 tandem MS (Thermo Fisher

Scientific, Waltham, MA, USA) with ESI operated in the positive ion mode.

Chromatographic separation was achieved on a 1.8 μm 4.6 x 50 mm (i.d.) Agilent ZORBAX Eclipse Plus C18 rapid resolution HT threaded column with an Alltech Direct-Connect Column 2 μm pre-filter (Deerfield, IL, USA) using gradient elution.[20] The MS/MS analysis was performed using selected reaction monitoring (SRM) of the protonated molecular ions for the analytes. The spray voltage was 4000 V, sheath gas (nitrogen) pressure 50 psi, capillary temperature 310° C, and collision pressure was 1.5 psi of high purity argon. Generation of detection data and integration of chromatographic peaks were performed by Xcalibur 2.0.7 Thermo Fisher Scientific (Waltham, MA, USA) LCquan 2.5.6 QF 30115 software.

Identification of the compounds was based on the presence of the molecular ion at the correct retention time, the presence of three transition ions and the correct ratio of these ions to one another (+/- 25% relative). The proven limit of quantitation (LOQ) was 5 ng/mL for all compounds. The limits of detection (LODs) for the compounds examined were comparable to results previously attained.[20]

Subjective effect measures

To quantify the various aspects of the subjective experience induced by DMT, participants were requested to answer two questionnaires measuring psychedelic-induced subjective effects. The first questionnaire was the Hallucinogen Rating Scale.[21] The HRS includes six subscales: (1) *Somaesthesia*, reflecting somatic effects; (2) *Affect*, reflecting emotional and affective responses; (3) *Volition*, indicating the incapacitation experienced; (4) *Cognition*, measuring modifications in thought processes or content; (5) *Perception*, measuring visual, auditory, gustatory and olfactory experiences; and finally (6) *Intensity*, which reflects the strength of the overall experience.

The second questionnaire was the States of Consciousness Questionnaire (SCQ). The SCQ was designed to assess mystical experiences. It includes seven subscales assessing seven different domains: (1) *Internal unity*, assessing the sense of pure awareness and a merging with ultimate reality; (2) *External unity*, assessing the experience of unity of all things; (3) *Transcendence of time and space*; (4) *Ineffability and paradoxicality* of the experience; (5) *Sense of sacredness* or awe caused by the experience; (6) *Noetic quality* assessing the experience of intuitive knowledge of ultimate reality; and finally the (7) *Deeply felt positive mood* measuring sensations of joy, peace, and love. The SCQ has proven sensitive to the effects of psychedelics.[22,23]

Statistics

Descriptive statistics (mean and standard deviation) were used to report the amounts of the different compounds measured. Percentages were calculated relative to the total amounts of DMT plus metabolites excreted expressed in micromoles.

Inferential statistics were also calculated to compare the DMT and metabolite percentages measured and the scores on the HRS and SCQ questionnaires between smoked and oral DMT. Within-group comparisons were carried out using the non-parametric Wilcoxon's test. Additionally, DMT and metabolite percentages were compared with data obtained in a previous study involving ayahuasca.[19] Between-study comparisons were carried out using the non-parametric Mann-Whitney test. Differences were considered statistically significant for p values <0.05.

Results and discussion

Subjective effects

Following smoked intake, all participants reported experiencing fully psychoactive effects of medium (five out of six participants) and high intensity (one out of six participants). This was in contrast with the oral administration where only one participant reported experiencing any effect at all and described it as being very low in intensity (he verbally described it as having an intensity of 1 on a scale from 1 to 10). As shown in Figure 2, scores on all subscales of the HRS and six of the seven subscales of the SCQ were significantly higher after smoked as compared to oral intake.

Scores on the Perception and Intensity subscales of the HRS were higher than those previously reported for a high ayahuasca dose equivalent to 1 mg DMT/kg body weight.[24] On the contrary, scores after oral intake were lower than those of the psychostimulant d-amphetamine.[24] Scores on the SCQ subscales were lower than those reported for a 30 mg/70 kg oral psilocybin dose.[22]

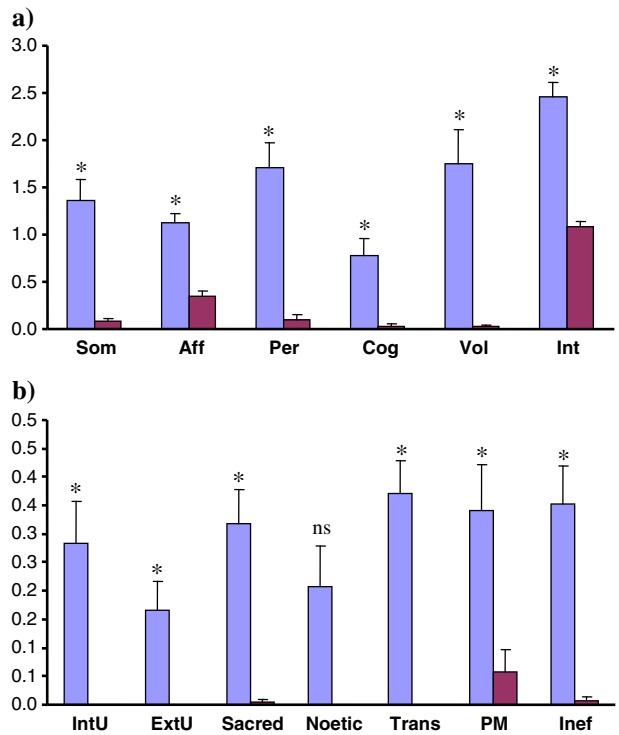

Figure 2. Scores on the different subscales of the HRS and SCQ questionnaires following smoked (blue) an oral (red) DMT intake: (**A**) HRS: Som = *Somaesthesia*, Aff = *Affect*, Per = *Perception*, Cog = *Cognition*, Vol = *Volition*, Int = *Intensity*; (**B**) SCQ: IntU = *Internal unity*; ExtU = *External unity*, Sacred = *Sense of sacredness*, Noetic = *Noetic quality*, Trans = *Transcendence of time and space*, PM = *Deeply felt positive mood*, Inef = *Ineffability and paradoxicality* of the experience. Statistical comparison between intake routes was conducted using Wilcoxon's test. $n = 6$, * $p < 0.05$, ns = not significant.

Urine determinations

Mean ± standard deviation urine volume collected was 1285 ± 302 mL after smoked DMT and 1377 ± 531 ml after oral DMT. These volumes did not differ statistically [$z = -0.732$, $p > 0.1$].

In the urine collected during the 24 h prior to each drug intake, concentrations for DMT and DMT-NO were below the LOD (limit of detection) but not for IAA which, as expected, is excreted physiologically. The individual amounts of DMT, DMT-NO and IAA measured following drug intake are presented in Table 1. As shown therein, the total amounts of DMT plus metabolites quantified in urine was larger after oral intake than after smoking [$z = -1.992$, $p = 0.046$]. These differences may reflect thermal degradation and incomplete vaporization and inhalation of DMT in the smoked route.

In order to control for the overall recovered amounts between routes while addressing the relative contribution of oxidative deamination and *N*-oxidation to DMT metabolism, we calculated the percentage of each metabolite relative to the overall substances measured in urine. Additionally, to control for physiological IAA, the amounts measured for each individual in the 24 h period prior to the drug sessions were subtracted from amounts after smoked and oral DMT. As shown in Table 1, following oral intake, unmetabolized DMT represented less than 1% of the total compounds found in urine. Interestingly, DMT-NO, the MAO-independent metabolite, amounted to 3%. The rest was IAA, indicating the predominance of oxidative deamination when DMT is taken by the oral route.

The analysis of the urine samples obtained following smoked DMT showed a higher proportion of unmetabolized DMT, which almost reached 10%. The distribution of the two metabolites showed a clearly different pattern as compared to the oral route. The percentage of DMT-NO increased to around 28% whereas that of IAA decreased to 63%. As shown in Figure 3, the statistical comparison between routes showed significant differences in the percentage of unmetabolized DMT and IAA. Though higher values were found for DMT-NO, the comparison was not significant due to the large intersubject variability observed following smoked DMT.

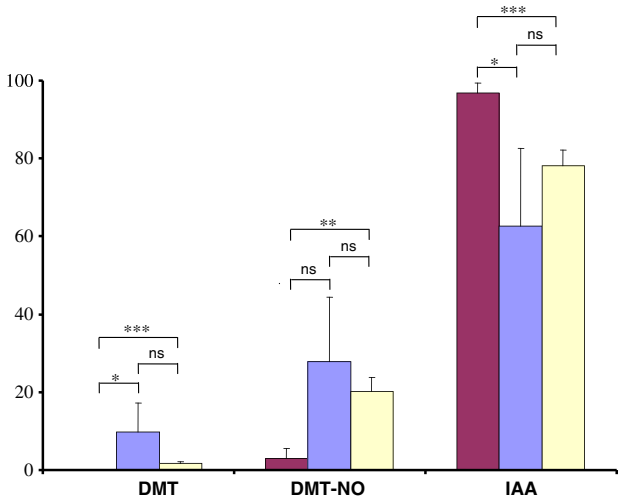

Figure 3. Graph showing percentage distributions of DMT, DMT-NO and IAA in human urine following smoked DMT (blue), oral DMT (purple) and ayahuasca (yellow, $n = 10$, data from a published study.[19]) Notice the absence of significant differences between smoked DMT and ayahuasca. Within-group comparisons using Wilcoxon's test and Between-group comparisons using Mann-Whitney test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ns = not significant.

For comparison purposes, Figure 3 shows the DMT and metabolite distribution in urine following ayahuasca. These results were obtained in a previous study by our group.[19] Similar to what we observed here following smoked DMT, after ayahuasca administration unmetabolized DMT (1.8%) was found in urine together with around 20% DMT-NO and 78% IAA. The comparison of the DMT and metabolite percentages measured after ayahuasca and after smoked DMT did not show any significant differences.

Table 1. Summary statistics and individual values of DMT and metabolite amounts (micromoles and percentage) measured for each study participant in 24 h urine after smoked and oral intake. IAA values have been corrected by subtracting the amounts (micromoles) measured in the 24 h urine collected prior to drug intake. Percent values refer to the total micromoles measured in each individual. SD = standard deviation

Subject Smoked	DMT µmol	DMT-NO µmol	IAA µmol	Total µmol	DMT %	DMT-NO %	IAA %
1	0.12	0.14	0.00	0.26	47.30	52.70	0.00
2	0.12	0.16	8.42	8.69	1.33	1.85	96.82
3	0.13	0.14	5.72	5.99	2.13	2.34	95.53
4	0.24	0.31	24.89	25.44	0.95	1.20	97.54
5	0.15	0.20	2.05	2.40	6.32	8.19	85.50
6	0.00	0.04	0.00	0.04	0.00	100.00	0.00
Mean	**0.13**	**0.16**	**6.85**	**7.14**	**9.67**	**27.71**	**62.61**
SD	**0.08**	**0.09**	**9.45**	**9.58**	**18.56**	**40.61**	**48.70**
Oral	µmol	µmol	µmol	µmol	%	%	%
1	0.00	0.29	43.60	43.90	0.00	0.67	99.33
2	0.00	0.21	16.92	17.12	0.00	1.20	98.80
3	0.15	0.04	66.37	66.57	0.23	0.07	99.71
4	0.00	0.30	57.15	57.45	0.00	0.52	99.48
5	0.00	0.32	1.78	2.10	0.00	15.30	84.70
6	0.00	0.29	53.14	53.42	0.00	0.53	99.47
Mean	**0.03**	**0.24**	**39.83**	**40.09**	**0.04**	**3.05**	**96.91**
SD	**0.06**	**0.10**	**25.17**	**25.16**	**0.09**	**6.01**	**5.99**

On the contrary, the comparison between percentages after ayahuasca and after oral DMT yielded significant differences for all three compounds (Figure 3).

As an additional analysis, we explored potential correlations between DMT, DMT-NO and IAA levels in urine after smoked DMT and scores on the subjective effects questionnaires. We found statistically significant inverse correlations between IAA and the SCQ *Internal unity* subscale. Correlations were significant when IAA was expressed as micromoles ($r = -0.894$, $r^2 = 0.798$, $p = 0.016$) and as percentage ($r = -0.894$, $r^2 = 0.798$, $p = 0.038$). Thus, the presence of smaller amounts of the main MAO-dependent metabolite of DMT was associated with more intense subjective effects. We also calculated the ratio between IAA and DMT-NO levels for each participant and we correlated these values with subjective effects measures. Again, an inverse correlation was found between this ratio and the *Internal Unity* subscale ($r = -0.919$, $r^2 = 0.845$, $p = 0.010$). The scatter plot for this correlation is shown in Figure 4. Trend correlations were also found for the *Sense of Sacredness* ($r = -0.795$, $r^2 = 0.632$, $p = 0.059$) and *Transcendence of time and space* ($r = -0.764$, $r^2 = 0.584$, $p = 0.077$) subscales. Though preliminary due to the small sample size, these results suggest that psychoactivity depends on the shift from oxidative deamination to *N*-oxidation. As the highly efficient MAO-dependent first-pass metabolism is circumvented by the smoked route, DMT metabolism is directed to the less efficient *N*-oxidation allowing the access of larger amounts of the parent compound to the central nervous system. This gives rise to the mystic-like experiences measured by the subscales of the SCQ.

In the present study we assessed the metabolism and urinary disposition of DMT administered by two different routes: orally and smoked. The absence of unmetabolized DMT following oral administration is compatible with an intense first-pass effect, as portal circulation conveys absorbed substances directly to the liver, where they undergo extensive biotransformation. By contrast, the smoked route initially bypasses the liver altogether and compounds typically do not suffer such intense metabolism. This would explain the greater levels of undegraded DMT found in this route.

Our results following oral DMT are in line with previous studies that found lack of psychoactive effects when DMT was administered orally in doses much higher than those in the present study.[25] Early studies had identified IAA as the degradation product of DMT in urine.[6] The high levels of IAA found in our study support the notion that MAO is the main metabolic route for DMT, as previously noted by other researchers.[17,18,26–30] This is also true for other methylated tryptamines,[30] for which the corresponding indoleacetic acid has been identified as the major breakdown product.[30–33] However, MAO-catalyzed oxidative deamination is not the only metabolic pathway available to these compounds, as DMT-NO was also formed, although in small amounts, following oral DMT intake.

In a previous study with ayahuasca, we also found that DMT-NO accounted for 20% of all tryptamine derivatives measured in urine.[19] We estimated an 80:20 ratio for IAA:DMT-NO, very close to the value found here after smoked DMT. Similar to what occurs after smoked DMT, in the presence of MAO-inhibiting harmala alkaloids, DMT metabolism becomes partially shifted from oxidative deamination to *N*-oxidation. Therefore, MAO inhibition or the use of routes of administration other than oral (smoking in this case) effectively enhance *N*-oxidation as an alternative pathway for the elimination of DMT. This shift has also been observed in *in vitro* studies where MAO is inhibited. The MAO-inhibitor iproniazid effectively blocks the formation of IAA from DMT in liver homogenates although not the formation of DMT-NO.[30] Iproniazid also increases tissue levels of DMT *in vivo* in the rat,[29] and urinary excretion of unmetabolized DMT and DMT-NO.[28] Considering these results and the negative correlation between IAA/DMT-NO ratio and subjective effects found in the present study, it appears that the metabolic shift is closely associated with the presence of psychoactive effects. Thus, low IAA and high DMT-NO values were associated with higher scores on the SCQ *Internal Unity subscale*. This instrument measures sensations that are considered characteristic of mystical experiences and can be induced by other psychedelics such as psilocybin.[22,23]

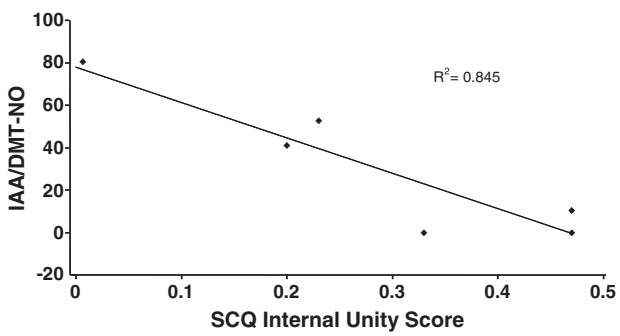

Figure 4. Scatter plot showing the inverse relationship between excreted IAA/DMT-NO ratio after smoked DMT and the intensity of subjective effects (SCQ *Internal unity* subscale).

Conclusion

In the present study we identified the main degradation products of DMT when the drug is taken alone by the oral and smoked routes. Oxidative deamination appeared to be the main degradation pathway for DMT in humans when administered *per os*. This route was associated with a total absence of psychoactive effects. On the other hand, smoked DMT was fully psychoactive and this route led to lower IAA levels and higher DMT-NO levels in urine. Furthermore, low levels of IAA and a low IAA/DMT-NO ratio after DMT smoking were associated with more intense subjective effects. The present findings show that in the smoked route a shift from MAO-dependent to less efficient CYP-dependent metabolism takes place. This shift is responsible for psychoactivity and is analogous to that observed in ayahuasca preparations combining DMT with MAO inhibitors.

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