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^{14}C-Psilocin tissue distribution in pregnant rats after intravenous administration

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ABSTRACT

Background: Many species of hallucinogenic mushrooms have been found in the genus *Psilocybe*. The main psychoactive chemicals of *Psilocybe* mushrooms are psilocin and its phosphoryloxy derivative, psilocybin. In addition to its psychedelic effects, psilocybin is an effective agent to lift the mood of depressed patients with terminal cancers.

Objective: To study the dispositional kinetics of ^{14}C-psilocin in pregnant rats after intravenous injection, to calculate tissue dose surrogates *i.e.*, tissue ^{14}C concentration and area under the concentration-time curve using the experimental data, to quantify trans-placental passage of psilocin and/or its metabolites, and to identify new psilocin metabolite(s) in rat urine.

Methods: A group of 15 pregnant Wistar rats weighing between 0.30-0.36 kg was used in the study. Each rat was given a single dose of 7.5 mg/kg ^{14}C-psilocin *i.v.* Three rats were randomly selected and sacrificed at 0.5, 1.0, 2.0, 4.0, and 8.0 hr post-dosing. The maternal and fetal tissues were quickly removed and the radioactivity in these tissues determined by liquid scintillation counting.

In a separate study, urine samples were collected from 6 male Wistar rats after administering 15 mg/kg of unlabeled psilocin *i.p.* The urine samples were collected and extracted by chloroform-methanol (9:1 v/v) and analyzed using a gas chromatograph/mass spectrometer.

Results: ^{14}C-Psilocin crossed the placental barrier of pregnant rats readily after *i.v.* administration; maternal tissue ^{14}C concentrations were found to be much higher than those in fetal tissues. The areas under the curve for maternal tissues also were much higher than the fetal tissues. In general, maternal tissues could be divided into the fast eliminating organ group, which

included the brain (elimination half-life <13 hr) and the slow eliminating organ group, which included all fetal tissues (elimination half-life >13 hr). A new psilocin metabolite tentatively identified as dihydroxyindoleacetic acid was found in the urine.

Conclusion: Our study showed that psilocin readily crossed the placental and blood-brain barriers of pregnant rats. Because psilocin was eliminated slowly from the fetal tissues of rats, human consumption of magic mushrooms should be avoided during pregnancy.

Key words: magic mushrooms, psilocin, placental barrier, pregnant rats

BACKGROUND:

Recreational use of indigenous *Psilocybe* mushrooms has become very popular in many parts of the world. Psilocin and its phosphoryloxy derivative, psilocybin, are the major psychoactive compounds of the hallucinogenic mushrooms [1]. Indeed, the psychedelic effect of psilocybin/psilocin is mediated mainly *via* the serotonin 5-HT_{2A} receptors [2] and may vary with the mushroom species, location of growth, and harvesting seasons.

The pharmacokinetics and tissue distribution of psilocybin/psilocin have been studied extensively in rodents [3, 4] and humans [5]. ^{14}C-Psilocin is absorbed rapidly by male rats after receiving a single dose orally [6]. After absorption, psilocin is distributed by the blood to the whole body and ^{14}C level in tissues is found to decrease in the order of kidney > liver > brain > blood. About 60% of the orally administered ^{14}C-psilocin was excreted in the urine and 21% in the feces within 1 day post-dosing. Significant amounts of psilocin also have been detected in the kidney, liver and brain of mice after receiving a single oral dose of psilocybin [3].

Psilocybin is rapidly hydrolyzed to psilocin by alkaline phosphatase or esterases in the gastrointestinal tract and/or liver [3, 6-8]. The fact that the phosphoric acid ester group of psilocybin is rapidly hydrolyzed indicates psilocin is the actual bioactive component of magic mushrooms and psilocybin merely acts as a pro-drug (Figure 1). Kalberer *et al*. [6] have reported that less than 4% of the psilocin administered to rats is metabolized to 4-hydroxy-3-indoleacetic acid (4-HIAA) and no glucuronide metabolites have been found in the rat study. In contrast, psilocin *O*-glucuronide is found in the serum of human volunteers dosed with psilocin orally [9]. Indeed, more than 80% of the psilocin administered to humans is metabolized to psilocin glucuronides. *In vitro* psilocin glucuronidation also has been studied using 19 recombinant human UDP glucuronosyltransferases of the subfamilies 1A, 2A and 2B [10]. Holzmann *et al*. [1] have shown that psilocin may undergo enzymatic oxidation in humans to form 4-hydroxytryptophole (4-HT) and 4-hydroxyindole-3-acetaldehyde, which may be further metabolized to 4-HIAA.

A recent study has shown that psilocybin is able to lift the moods of patients with advanced-stage cancer at a moderate dose of 0.2 mg/kg [11]. The mechanism of anti-depression effect is not fully understood, but psilocybin is able to lower the elevated medial prefrontal cortex activity in patients suffering from depression. The anti-depression effect of psilocybin also is explainable by an increased emotional insight of the depressed patients after lowering their psychological

defense [12]. In addition to its anti-depression effect, psilocybin has been used to induce schizophrenic psychosis in healthy volunteers [13, 14].

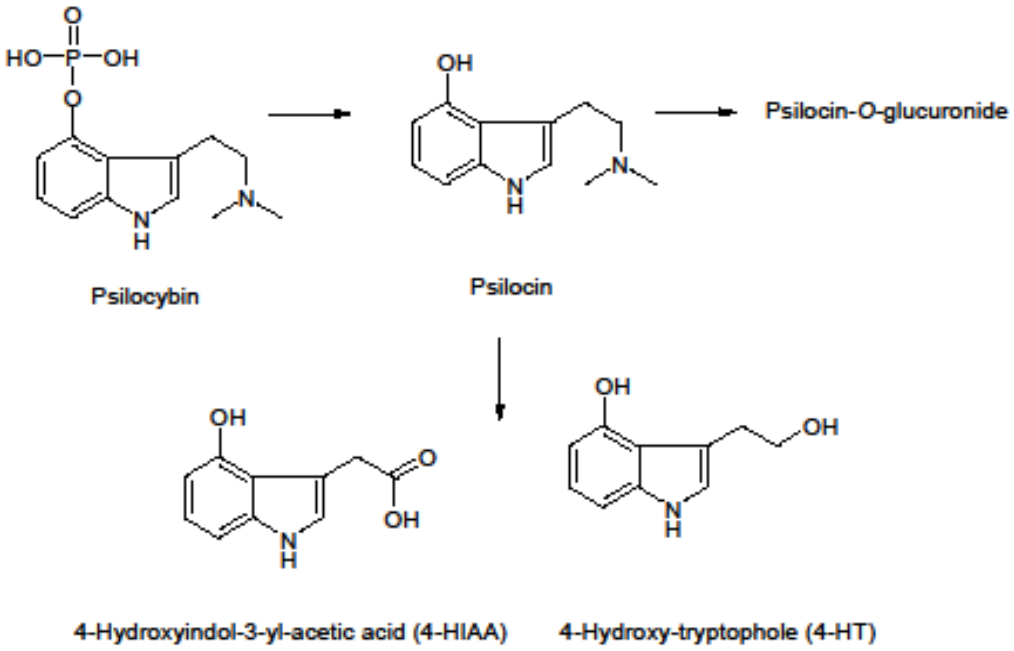

Figure 1. Psilocybin and psilocin biotransformation

Despite the widespread use of *Psilocybe* mushrooms [15-18], very little is known of the dispositional kinetics and the tissue dose [19] of psilocin in pregnant animals. Andersen [19] has reported that tissue concentrations and areas under the curve ($AUC_{0\text{-last}}$) of a drug from pharmacokinetic studies can be used as quantitative measures of tissue dose which may be unattainable by direct experimentation. The objectives of this study were to study the dispositional kinetics of ^{14}C-psilocin in pregnant rats after intravenous injection, to calculate tissue dose surrogates *i.e.*, tissue ^{14}C concentration and $AUC_{0\text{-last}}$ using the experimental data, to quantify trans-placental passage of psilocin and/or its metabolites, and to present preliminary findings on the identity of a new psilocin metabolite in rat urine. In view of the potential use of magic mushrooms as an anti-depressant in humans, it is important to study the placental transfer of psilocin in pregnant animals. As tissue dose is a measure of the intensity of tissue exposure to psilocin [19], the present study will provide the information needed to evaluate the effectiveness and safety of psilocin in humans.

MATERIALS AND METHODS:

Chemicals: Unlabeled psilocin was a product of Sandoz Pharmaceutical Ltd. (Basel, Switzerland). Chemical purity of unlabeled psilocin was >99%. ^{14}C-Labeled psilocin (specific activity 0.0878 μCi/mg) was synthesized chemically in our laboratory according to Poon *et al.* [20]. Radiochemical purity of ^{14}C-psilocin was determined to be >98%. A license was obtained from Health Canada for the synthesis, storage and handling of the Schedule 1 drug. A solution of ^{14}C-labeled psilocin was prepared by mixing ^{14}C-labeled psilocin and unlabeled psilocin together

in distilled water such that the administration of 0.5 ml of the solution provided the desired dose of the test chemical.

Animals: Fifteen pregnant Wistar rats weighing between 300-365 g (days 19-20 of gestation) and 6 male Wistar rats weighing between 250-300 g were purchased from Charles River Canada Inc. (St., Constant, Quebec). They were acclimatized in the Animal Care Facility of Simon Fraser University for 1 week before use. Commercial laboratory rat chow and water were provided *ad libitum.* The procedure associated with animal care and experimentation was conducted with the approval of the Animal Care Committee at Simon Fraser University.

Animal treatment: The tissue distribution study was initiated by injecting ^{14}C-psilocin (7.5 mg/kg) *i.v.* to each of the 15 pregnant rats. Three rats were randomly selected from the group and sacrificed at specific time points post-dosing (0.5, 1.0, 2.0, 4.0, and 8.0 hr). Maternal blood and tissue specimens (*e.g.*, liver, kidney, lung, heart, spleen, brain, and muscle) were removed immediately from the rats. The fetuses were delivered via hysterectomy, and fetal blood, liver, lung, kidney, and heart samples were removed. All maternal and fetal tissue samples were stored at -10 ^{o}C until analysis.

Urine samples were collected from 6 male Wistar rats after receiving a single dose of unlabeled psilocin (15 mg/kg) *i.p*. The rats were kept in separate metabolic cages and the urine was collected daily for two days. The urine samples were pooled and stored at -10 ^{o}C for subsequent analysis. Control urine was collected from the rat prior to psilocin administration.

Determination of radioactivity in tissues and biologic fluids: Blood samples were digested at 50 ^{o}C for 30 min in separate liquid scintillation vials containing 1 ml Protosol:ethanol (1:1 v/v). The vial was cooled, decolorized with 30 % hydrogen peroxide (0.5 ml) and neutralized by 0.5 N HCl (0.5 ml). After the addition of Biofluor (14 ml), the radioactivity in the vial was determined by a Beckman LS-8000 Liquid Scintillation Counter. ^{14}C concentration in blood was expressed as µg psilocin equivalents/ml blood.

Tissue samples (0.5 -1.0 g) were weighed accurately on a piece of filter paper. The tissue was oxidized in a Tri-Carb B306 Sample Oxidizer (Packard Co., Downers Grove, Ill.). The $^{14}CO_2$ evolved from burning the tissue was trapped in 6 ml of Carbo-Sorb in a liquid scintillation vial. After the addition of Permafluor (14 ml), the vial was counted by a LSC. ^{14}C concentration in tissue was expressed as µg psilocin equivalents/g tissue wet weight.

Data analysis: Tissue/blood ^{14}C concentration data were plotted semi-logarithmically against the time of sample collection. The resulting concentration-time curves were analyzed using the non-compartmental approach of WinNonlin® pharmacokinetic package (V1.0, SCI software, Cary, North Carolina) to determine the $t_{1/2\beta}$ and $AUC_{0\text{-last}}$ (from 0 hour to the last time point) for each rat. $AUC_{0\text{-last}}$ was calculated by the trapezoidal method. The mean $\pm$ SD values of $t_{1/2\beta}$ and $AUC_{0\text{-last}}$ were calculated from three rats.

Isolation and characterization of urinary metabolites: The urine sample was thawed, rendered basic with $NaHCO_3$, and extracted 3 times with diethyl ether to remove the unchanged psilocin. The remaining aqueous layer was acidified to pH 3 by HCl and extracted 3 times by chloroform-methanol (9:1 v/v). The chloroform-methanol extracts were combined and dried under a gentle stream of nitrogen. The residues were re-dissolved in methanol and transferred to a 1000 μm thickness silica gel GF preparative TLC plate (20 X 20 cm Uniplate; Analtech Inc., Newark, DE) which was double-developed in $CHCl_3$:CH_3OH (9:1 v/v) to obtained good band separation. The psilocin metabolites were located by placing the plate under the UV light. The silica in the area containing the unknown metabolite was scrapped off from the plate and extracted 3 times with chloroform:methanol (1:1 v/v). The extracts were combined and dried under a stream of nitrogen. The residues were analyzed by direct probe mass spectrometry operated under the electron impact mode and at an ionization potential of 70 eV. The ion source was set at 200 ^oC. Mass spectral service was provided by the Department of Chemistry, Simon Fraser University.

RESULTS:

Figure 2 shows the mean ^{14}C (psilocin plus metabolites) concentrations *versus* time curves in the maternal and fetal blood of the pregnant rats. Maximal ^{14}C concentrations were observed in the maternal and fetal blood at 0.5 hr (the first time point of sampling) after injecting ^{14}C-psilocin *i.v.* to the rats. Both ^{14}C concentration-time profiles showed a rapid, biphasic decline of ^{14}C concentration with time. The maternal and fetal blood profiles appeared parallel to each other with maternal blood ^{14}C concentration 2.0-2.5 fold higher than fetal blood. The mean $AUC_{0\text{-last}}$ of the blood concentration-time curves, which represented psilocin doses in the maternal and fetal blood, were 28.4 $\pm$ 3.7 and 12.7 $\pm$ 4.1 μg psilocin equivalents·hr/ml, respectively. The elimination half-life ($t_{1/2\beta}$) of ^{14}C in the maternal and fetal blood curves was 19.8 $\pm$ 2.6 and 14.9 $\pm$ 4.7 hr, respectively.

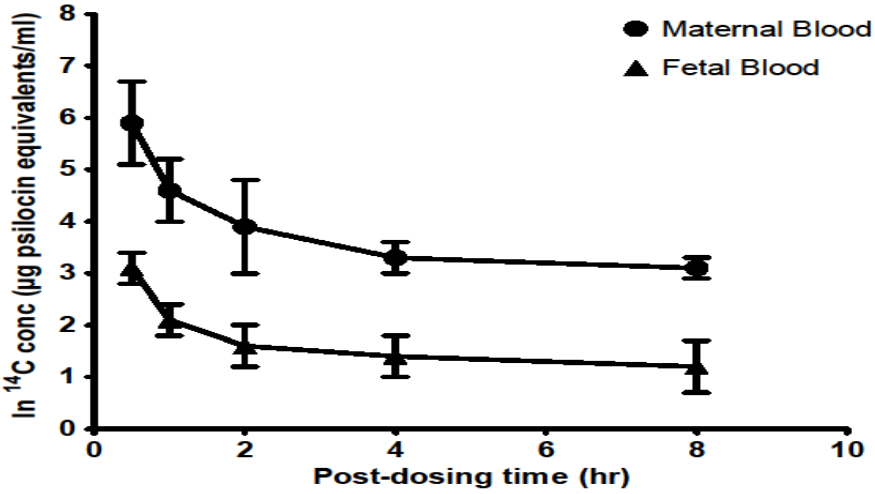

Figure 2. Mean ^{14}C concentration *versus* time curves for maternal and fetal blood in pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

Figures 3, 4, 5 and 6, respectively show the time course of ^{14}C concentrations in the liver, lung, heart, and kidney of the pregnant rats. As with the blood concentration-time curve (Figure. 2), ^{14}C levels in the maternal organs were much higher than the fetal tissues.

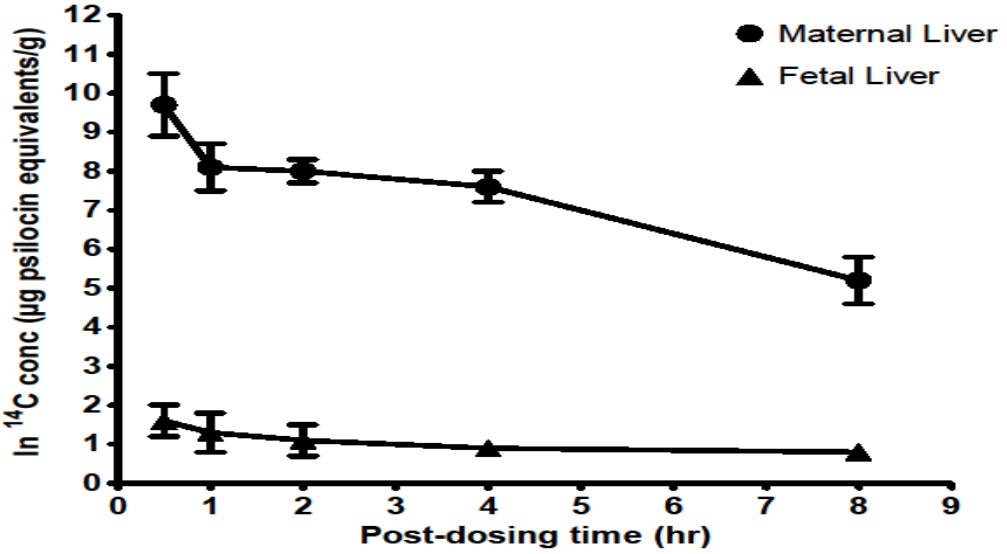

Figure 3. Mean ^{14}C concentration *versus* time curves for maternal and fetal liver in pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

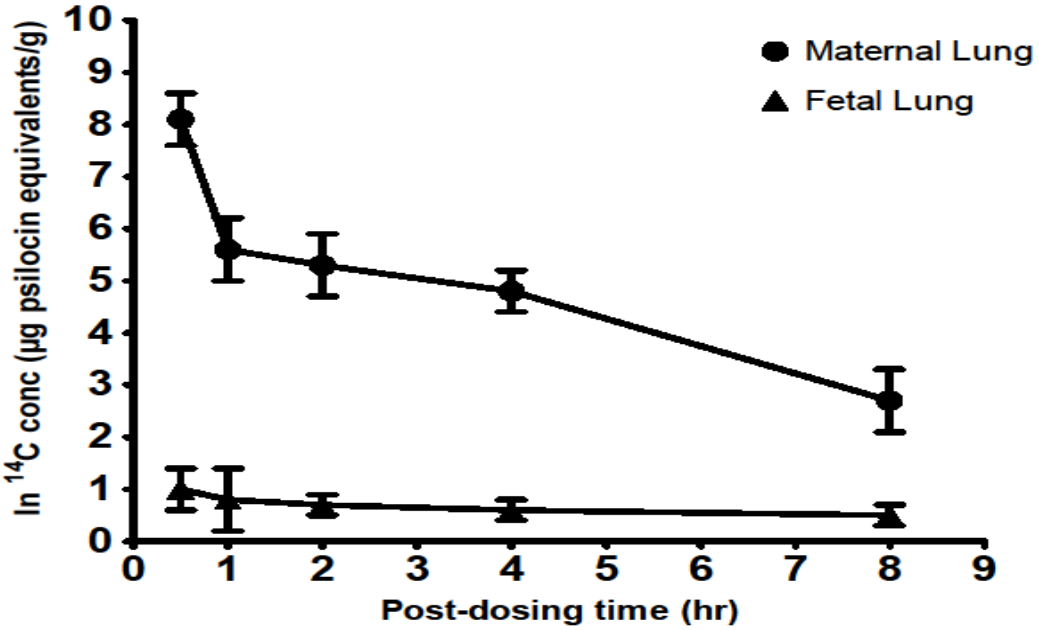

Figure 4. Mean ^{14}C concentration *versus* time curves for maternal and fetal lung in pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

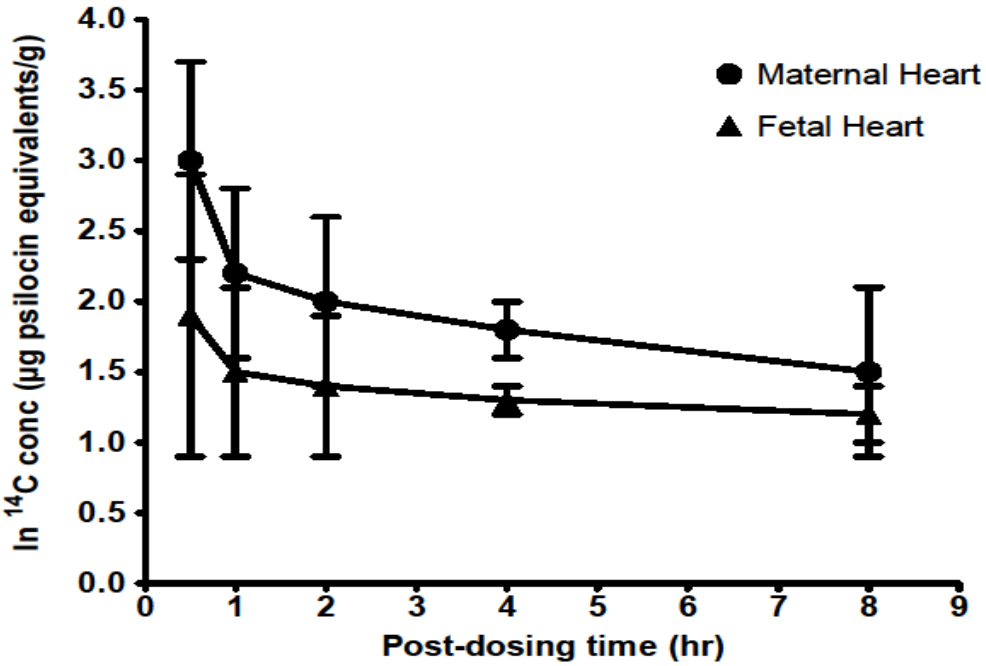

Figure 5. Mean ^{14}C concentration *versus* time curves for maternal and fetal heart in pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

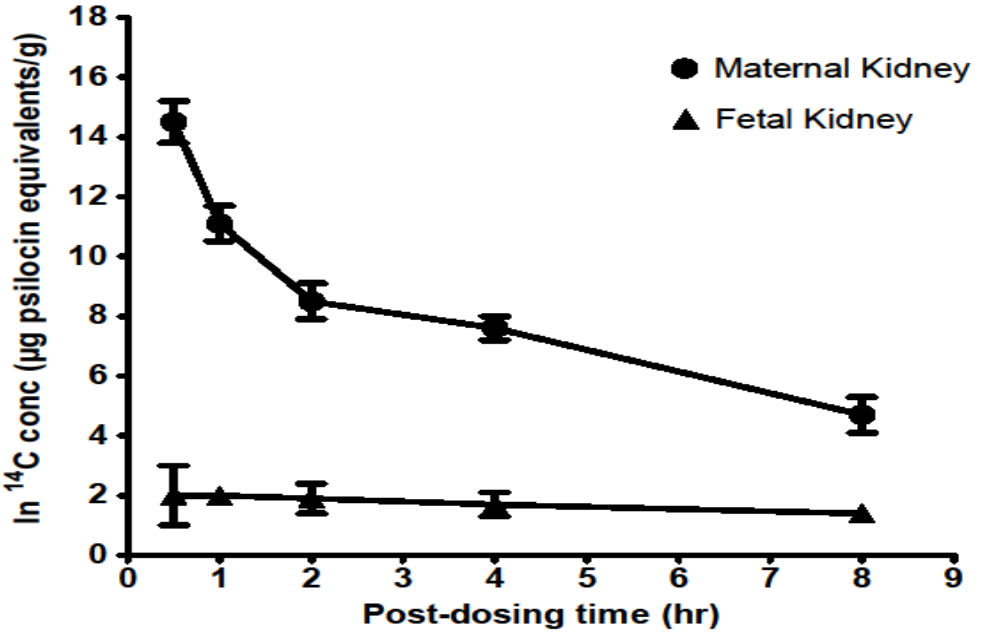

Figure 6. Mean ^{14}C concentration *versus* time curves for maternal and fetal kidney in pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

The time course of psilocin-derived radioactivity in maternal spleen and muscle are depicted in Figure 7. The time course of psilocin-derived radioactivity in maternal brain and placenta are shown in Figure 8.

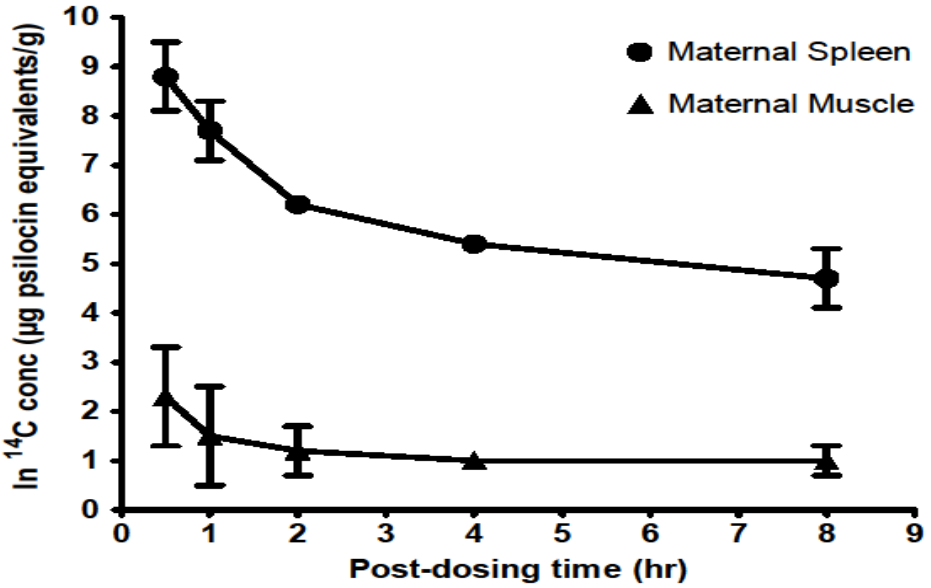

Figure 7. Mean ^{14}C concentration *versus* time curves in maternal spleen and muscle of pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

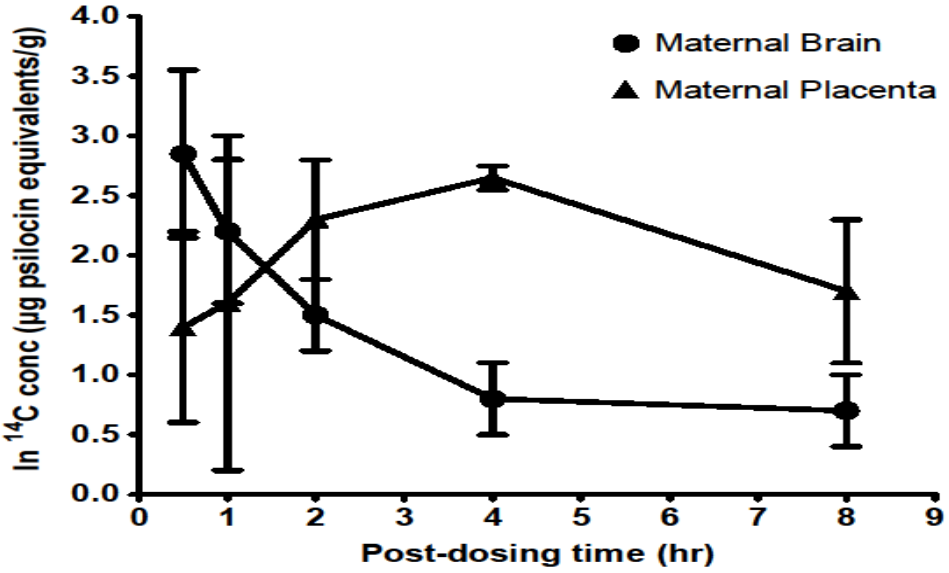

Figure 8. Mean ^{14}C concentration *versus* time curves in maternal brain and placenta of pregnant rats after receiving an *i.v.* injection of 7.5 mg/kg ^{14}C-psilocin. Error bars represent the standard deviation of three rats.

Mean ^{14}C concentrations in the spleen, muscle and brain were the highest at 0.5 hr post-dosing (the first time point of sampling) (Figures 7 and 8). However, ^{14}C levels in the placenta increased slowly to a maximum at about 4 hr post-dosing before decreasing with time (Figure 8).

Mean ^{14}C $AUC_{0\text{-last}}$ in maternal and fetal tissues is summarized in Figure 9. All maternal tissues had much higher mean $AUC_{0\text{-last}}$ than the fetal tissues. Based on the results of these studies, the maternal tissues could be divided into the large $AUC_{0\text{-last}}$ organ group with ≥13 µg psilocin equivalents·hr/ml: blood, liver, lung, kidney, spleen, heart and placenta and the small

$AUC_{0\text{-last}}$ organ group with <13 µg psilocin equivalents·hr/ml: muscle, brain, and fetal tissues (Figure 9).

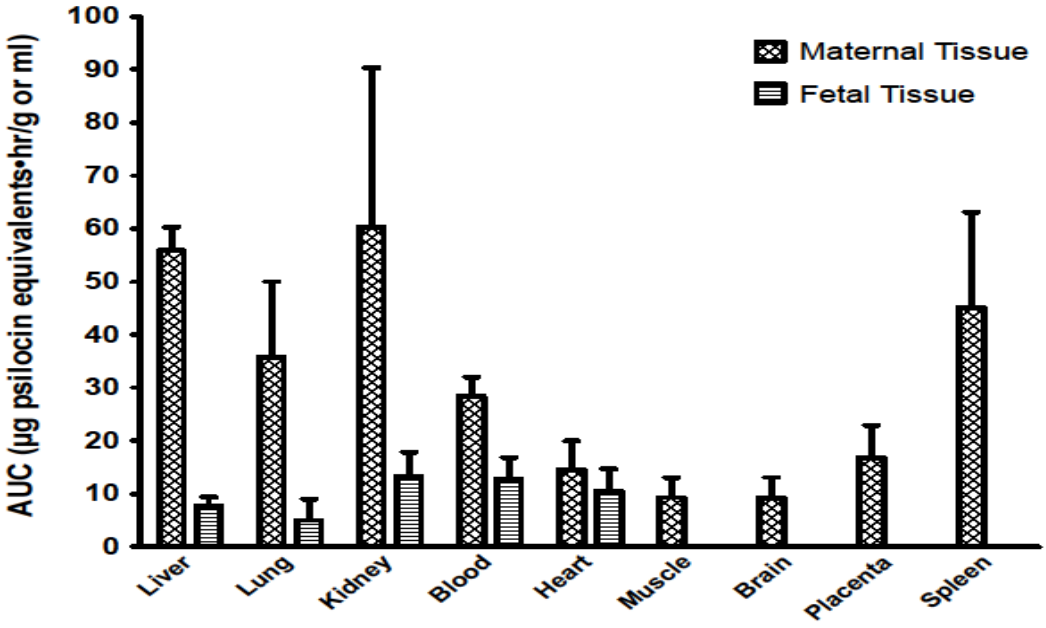

Figure 9. Mean area under the concentration-time curves of various maternal and fetal tissues. Values represent the means ± SD of three different rats; error bars up represent positive standard deviations.

The $t_{1/2\beta}$ of ^{14}C-psilocin in maternal and fetal tissues is summarized in Figure 10. The $t_{1/2\beta}$ of maternal lung, liver, kidney, brain and placenta were relatively short (<13 hr); they might be classified as fast eliminating organs. In contrast, the $t_{1/2\beta}$ of maternal heart, muscle, spleen, blood and fetal tissues were relatively long (>13 hr); they might be classified as slow eliminating organs.

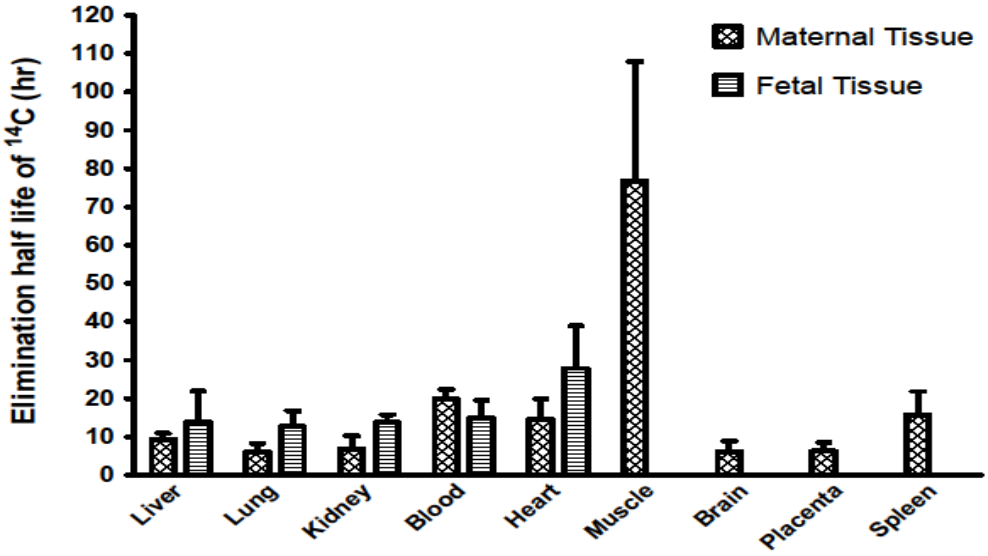

Figure 10. Half-lives of ^{14}C elimination from maternal and fetal tissues. Values are the means ± SD from of three different rats; error bars up represent the positive standard deviation.

Cumulative ^{14}C excretion in rat urine at 4 hr and 8 hr post-dosing were 33.2% and 35.9% of the administered dose, respectively. These findings showed that the majority of the psilocin-derived radioactivity was excreted in the urine during the first 4 hr of post-dosing period.

An unknown metabolite of psilocin was detected in the chloroform-methanol extract of the urine; it had a R_f of 0.6 on the TLC plate developed in $CHCl_3$:CH_3OH (9:1 v/v). The unknown metabolite was not found in the urine of untreated rats. The mass spectral data of the unknown metabolite showed the following prominent fragmentation ions (relative intensities %): 207(100), 189(75), 177(28), 167(75), 130(57), 105(70), 91(75). The fragmentation pattern and the molecular ion $(M)^+$ at m/z 207 were consistent with the molecular formula of $C_{10}H_9O_4N$ which indicated a dihydroxyindoleacetic acid or its keto form.

DISCUSSION:

To our knowledge, this is the first study in which the dispositional kinetics of psilocin is investigated in pregnant rats following *i.v.* administration. Our results show psilocin readily crosses the blood-brain and placental barriers of pregnant rats, a finding which is consistent with psilocin being a small molecule with an octanol-water partition coefficient of 1.45 [21]. After crossing the placental barrier, psilocin distributes rapidly to the various fetal tissues. Psilocin likely crosses the blood-brain and placental barriers by passive diffusion since a concentration gradient is maintained between the maternal and fetal tissues throughout the study (Figures 2-6).

In the present study, tissue ^{14}C concentration and mean $AUC_{0\text{-last}}$ have been used as quantitative measures of tissue exposure to psilocin [19]. Our results show that the $AUC_{0\text{-last}}$ of maternal tissues is much higher than the fetal tissues (Figure 9). These are consistent with the ^{14}C concentration data in maternal and fetal tissues (Figures 2-6). In the present study, the kidney $AUC_{0\text{-last}}$ is the highest. This is followed by the $AUC_{0\text{-last}}$ of liver, brain, and blood in descending order. It should be noted that although the brain $AUC_{0\text{-last}}$ is low, it is related directly to the psychedelic and/or toxic effects of psilocin in animals (Figure 10).

Kalberer *et al*. [6] have reported that tissue ^{14}C concentration decreases in the order of kidney > liver > brain > blood after administering ^{14}C-psilocin to male rats *i.v*. Our results are in agreement with their findings. In contrast, tissue ^{14}C concentration decreases in the order of liver > kidney > adrenal > brain after administering ^{14}C-psilocin to male rats *p.o.* [6]. Clearly, the route of administration plays an important role in tissue ^{14}C concentration as ^{14}C-psilocin administered by the oral route is metabolized by the gastrointestinal tract and liver before being distributed to other organs whereas ^{14}C-psilocin administered by the intravenous route is distributed to other organs first before reaching the liver. As a result, hepatic ^{14}C concentration is the highest after *p.o.* administration of ^{14}C-psilocin [6] and renal ^{14}C concentration is the highest after *i.v.* administration (Figure 9).

Using ^{14}C-psilocin in the present study complicates our efforts to obtain a precise pharmacokinetic analysis of psilocin in the pregnant rats because unchanged psilocin cannot be easily separated from its metabolites and quantified. However, the $t_{1/2\beta}$ of ^{14}C concentration in the maternal tissues most likely is defined by the time course of psilocin glucuronide concentration [22]. Thus, the highly perfused and active metabolic organs (*i.e.*, maternal liver, lung, brain, kidney, and placenta) have relatively short $t_{1/2\beta}$ (<13 hr) and the slowly perfused and less active

metabolic organs (*i.e.*, maternal blood, heart, spleen, muscle and all fetal tissues) have relatively long $t_{1/2\beta}$ (>13 hr) (Figure 10). A comparison of the concentration-time profiles also shows that maternal tissue ^{14}C declines at faster rates than fetal tissue ^{14}C (Figures 3-6). An explanation for the slow decline of ^{14}C in the fetal tissues is not readily available but may be related to the underdeveloped mixed-function oxidase and monoamine oxidase enzymes in the fetuses. As such, the $t_{1/2\beta}$ of ^{14}C concentration in the fetal tissues most likely is defined by the time course of unchanged psilocin concentration rather than psilocin glucuronide concentration.

The mass spectral data show that the unknown metabolite in rat urine has a molecular ion $(M)^+$ at m/z 207. The fragmentation ions at m/z 189 ($C_{10}H_7NO_3$), 177 ($C_9H_7NO_3$), 167 ($C_7H_5NO_4$), 130 (C_8H_4NO), 105 (C_6H_3NO) and 91 (C_6H_3O) probably are resulted from $(M\text{-}OH, H)^+$, $(M\text{-}COH, H)^+$, $(M\text{-}C_3H_3, H)^+$, $(M\text{-}OH, CH_2COOH, H)^+$, $(M\text{-}CHCOH, CH_2COOH, H)^+$, and $(M\text{-}CCH_2COOH, NHCOH, H)^+$, respectively. The m/z 177, 167, and 105 fragments are formed by cleaving the aromatic ring from the psilocin molecule, and the m/z 91 fragment probably is formed by eliminating the pyrrole ring. These results are consistent with the structure of a dihydroxyindoleacetic acid and/or its keto isomer both of which are the oxidation product of 4-HIAA. We are unable to detect any 4-HIAA in the urine of rats after administering psilocin *i.v.* However, Kalberer *et al.* [6] have reported the presence of 4-HIAA in the urine of rats after *p.o.* administration. Hasler et al. [23] also have been unable to detect 4-HIAA in the plasma of humans after intravenous administration of psilocin but are able to detect it in the plasma after oral administration. Our results are consistent with the findings in their studies.

CONCLUSION:

Psilocin and/or its metabolite(s) are able to cross the placental barrier of pregnant rats by passive diffusion. In view of the potential use of psilocybin as an anti-depressant, it is important to study the pharmacokinetics and tissue distribution of psilocin in pregnant rats. Because psilocin is eliminated slowly from the fetal tissues, consumption of magic mushrooms by humans should be avoided during pregnancy.

List of abbreviations:

GC-MS, gas chromatography-mass spectrometry; TLC, thin layer chromatography; R_f, retention factor; $t_{1/2\beta}$, elimination half-life; $AUC_{0\text{-last}}$, area under the concentration-time curve from 0 to last time point; 4-HIAA, 4-hydroxy-3-indoleacetic acid; 5-HT receptors, 5-hydroxytryptamine receptors; *i.v.*, intravenously; *i.p.*, intraperitoneally; ln, natural logarithm.

Competing interests:

The authors report no conflicts of interest related to the contents of this article.

Authors' contributions:

FCPL conceived and designed this project. GP was responsible for synthesizing ^{14}C-labeled psilocin. YCC and SXH were responsible to conduct the experiments, data collection, figure generation. All authors participated in writing and publishing of the paper.

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REFERENCES:

1. Holzmann PP: Bestimmung van Psilocybin-Metaboliten im Humanplasmaund -min. PhD Thesis, Eberhard-Karls-Universifat, Tubingen, Germany; 1995.
2. Presti D, Nichols D: Biochemistry and neuropharmacology of psilocybin mushrooms. In: Teonanacatl: Sacred Mushroom of Vision. Edited by Metzner R. El Verano, Ca: Four Trees; 2004:89-108.
3. Horita A: Some biochemical studies on psilocybin and psilocin. J Neuropsychiat 1963, 4:270-273.
4. Aboul-Enein HY: Psilocybin: a pharmacological profile. Am J Pharmacy 1974, 91-95.
5. Hasler F, Bourquin D, Brenneisen R, Bar T, Vollenweider FX: Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. Pharm Acta Helv 1997, 72(3):175-184.
6. Kalberer F, Kreis W, Rutschmann J: The fate of psilocin in the rat. Biochem Pharmacol 1962, 11:261-9.
7. Horita A, Weber LJ: Dephosphorylation of psilocybin to psilocin by alkaline phosphatase. Proc Soc Exp Biol Med 1962, 106:32-34.
8. Eivindvik K, Rasmussen KE: Handling of psilocybin and psilocin by everted sacs of rat jejunum and colon. Acta Pharm Nord 1989, 1:295-302.
9. Kamata T, Nishikawa M, Katagi M, Tsuchihashi H: Direct detection of serum psilocin glucuronide by LC/MS and LC/MS/ MS: time-courses of total and free (unconjugated) psilocin concentrations in serum specimens of a 'magic mushroom' user. Forensic Toxicol 2006, 24:36–40.
10. Manevski N, Kurkela M, Höglund C *et al.*: Glucuronidation of psilocin and 4-hydroxyindole by the human UDP-glucuronosyltransferases. Drug Metab Dispos 2010, 38(3):386–395.
11. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR: Pilot Study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011, 68:71-78.
12. Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiotas T, Hobden P, Sharp DJ, Evans J, Feilding A, Wise RG, Nutt DJ: Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. British J Psych 2012, 200:238–244.
13. Vollenweider FX, Antonini A, Scharfetter C, Angst J, Leenders, KL: Hyperfrontality and psychopathology in the acute ketamin and psilocybin model of schizophrenia using PET and FDG. J Neurol 1994, 241:262.
14. Hermle L, Spitzer M, Borchardt D, Gouzoulis E: Beziehungen der Modell - bzw Drogenpsychose zu schizophrenen Erkrankungen. Fortschr Neurol Psychiat 1992, 60:383-392.

15. U.S. Alcohol, Drug Abuse and Mental Health Administration. The National Clearinghouse of Drug Abuse Information. 1973, Series 16. No.1.
16. van Poorten JF, Stienstra R, Dworacek B, Moleman P, Rupreht J: Physostigmine reversal of psilocybin intoxication. Anesthesiology 1982, 56(4):313
17. Gartz J., Allen JW., Merlin, MD: Ethnomycology, biochemistry and cultivation of psilocybe samuiensis Guzman, Bandala and Allen, a new psychoactive fungus from Koh Samui, Thailand. J Ethnopharmacol 1994, 43:73-80.
18. Marcano V., Marales M.A., Castellano F., Salazar F.J., Martiner L: Occurrence of psilocybin and psilocin in psilocybe pseudobullacea (Petch) Pegler from the Venezuelan Andes. J Ethnopharmacol 1994, 43:157-9.
19. Andersen M E: (1987) Tissue dosimetry in risk assessment, or what's the problem here anyway? In Pharmacokinetics in Risk Assessment, Drinking Water and Health. Edited by Gillette JR and Jollow DJ. Washington, D.C: National Academy Press; 1987:8-23.
20. Poon G, Chui YC, Law FCP: Synthesis of psilocin labelled with ^{14}C and ^{3}H. J Labelled Comp Radiopharmaceut 1986, 23:167-74.
21. Migliaccio GP, Shieh TL, Byrn SR, Hathaway BA, Nichols DE: Comparison of solution conformational preferences for the hallucinogens bufotenin and psilocin using 360-MHz proton NMR spectroscopy J Med Chem 1981, 24:206-209.
22. Gessner PK, Khairallh PA, McIsaac WM, Page IH: The relationship between the metabolic fate and pharmacological actions of serotonin, bufotenine and psilocybin. J Pharmacol 1960, 130:126-133.
23. Hasler F, Bourquin D, Brenneisen R, Bar T, Vollenweider FX: Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. Pharmaceutics Acta Helvetiae 1997, 72:175-184