Kinetics of L-Theanine Uptake and Metabolism in Healthy Participants Are Comparable after Ingestion of L-Theanine via Capsules and Green Tea[1–4]

Lisa Scheid,[5] Sabine Ellinger,[5]* Birgit Alteheld,[5] Hannes Herholz,[6] Jörg Ellinger,[7] Thomas Henn,[8] Hans-Peter Helfrich,[9] and Peter Stehle[5]

[5]Department of Nutrition and Food Science-Nutritional Physiology, University of Bonn, Bonn, Germany; [6]Department of Surgery, and [7]Department of Urology and Children Urology, University Hospital Bonn, Bonn, Germany; and [8]TeeGschwendner, Meckenheim, Germany; and [9]Institute for Numerical Simulation, University of Bonn, Bonn, Germany

Abstract

L-Theanine, an amino acid in green tea, is suggested to improve cognition and mood. Therefore, L-theanine is available as a supplement and is now used as an ingredient in functional drinks. Because data on the metabolic fate of L-theanine from human studies are lacking, we investigated the kinetics of L-theanine uptake and its metabolites, ethylamine and glutamic acid, in healthy participants. Within a randomized crossover study, 12 participants ingested a bolus of 100 mg L-theanine via capsules or green tea. On further occasions, 3 participants received 50 and 200 mg L-theanine via capsules. Blood and urine were collected before and up to 24 h postconsumption to determine the concentrations of L-theanine, proteinogenic amino acids, and ethylamine in plasma, erythrocytes, and urine by HPLC. L-Theanine increased in plasma, erythrocytes, and urine with comparable results after both treatments. The maximum plasma concentration of L-theanine occurred 0.8 h after intake of 100 mg L-theanine via capsules (24.3 ± 5.7 μmol/L) and tea (26.5 ± 5.2 μmol/L), respectively. The AUC of L-theanine in plasma increased dose dependently after intake of 50, 100, and 200 mg L-theanine via capsules. Moreover, ethylamine and glutamic acid increased in plasma and were excreted by urine after intake of capsules and tea. In conclusion, L-theanine is rapidly absorbed and seems to be hydrolyzed to ethylamine and glutamic acid. A minor part of L-theanine is retained in erythrocytes. Kinetics and urinary excretion of L-theanine, ethylamine, and glutamic acid are comparable after both treatments. Thus, functional effects of L-theanine intake may result from L-theanine, ethylamine, or glutamic acid.   J. Nutr. 142: 2091–2096, 2012.

Introduction

L-Theanine (γ-glutamylethylamide) is a nonproteinogenic amino acid occurring in tea leaves (*Camellia sinensis*) (1) and mushrooms (*Xerocomus badius*) (2). In tea leaves, L-theanine accounts for >50% of the total free amino acids (3). A serving size of 250 mL green tea prepared under the recommended brewing conditions provides ~40 mg L-theanine (4). Green and black tea are considered as major sources of L-theanine in the human diet,

because tea is the most consumed beverage besides water worldwide (5). Recently, L-theanine has gained popularity, because its intake is suggested to improve cognition and mood (6,7). Therefore, L-theanine is available as a nutritional supplement and is now used as an ingredient in functional drinks.

In rats, oral as well as i.g. administration of isolated L-theanine led to its temporary increase in plasma, liver, brain, and urine. This was followed by raised concentrations of ethylamine and glutamic acid in plasma and urine, probably due to hydrolysis of L-theanine (8,9). Moreover, L-theanine intake increased the brain concentrations of dopamine and γ-aminobutyric acid (6), which are suggested to reduce anxiety and improve mood (10).

In humans, a bolus intake of isolated L-theanine in doses between 50 and 200 mg increased the alpha brain wave activity detected by electroencephalography, indicating relaxation (11). The ingestion of 200–400 mg isolated L-theanine reduced self-reported anxiety and stress in healthy participants (7) and schizophrenia patients (12), respectively. Furthermore, L-theanine is reported to improve attention and cognitive performance

synergistically with caffeine (7,11). In a recent trial, van der Pijl et al. (13) observed an increase of L-theanine in the plasma of healthy men after an intake of 25, 50, and 200 mg L-theanine provided via an aqueous solution or black tea.

However, data on the metabolic fate of L-theanine from human studies are lacking. Thus, the present study investigated the kinetics of L-theanine uptake and its metabolites, ethylamine and glutamic acid, in plasma and erythrocytes as well as its urinary excretion after a bolus intake of capsules and green tea in healthy participants.

Materials and Methods

Chemicals and reagents. L-Theanine, proteinogenic amino acids, and ethylamine were obtained from Sigma-Aldrich, acetonitrile and methanol (both HPLC grade) from Roth, and o-phthalaldehyde, β-mercaptoethanol, and further reagents were purchased from Serva.

Participants. Twelve healthy nonsmokers (6 women, 6 men) with a mean age of 29 y (range: 26–39 y) and a mean BMI of 22.3 kg/m^2 (range: 20.2–24.6 kg/m^2) participated in this study. The inclusion criteria were age between 18 and 40 y, nonsmoking, and normal weight [BMI between 18.5 and 24.9 kg/m^2 (14)]. The exclusion criteria were any known diseases, pregnancy, lactation, the use of dietary supplements, any medication (except contraceptives), and blood donation 30 d prior to or during the study. Inclusion and exclusion criteria were checked by questionnaire.

Study design. Within a randomized crossover trial, participants ingested a bolus of 100 mg L-theanine, either in isolated form via capsules or via 250 mL green tea, after a 12-h overnight fast. On further occasions, 3 participants received an additional bolus of 50 and 200 mg L-theanine via capsules. All treatments were separated by a washout period of at least 2 wk. Randomization was done by lot and all samples were coded to allow test evaluation on blinded samples.

To avoid artifacts by L-theanine intake from other sources, the participants were instructed to refrain from consuming tea, tea-based products, and mushrooms 3 d before the study until completion. On each study day, participants fasted for 3 h after treatments. Food intake was documented by self-completed dietary records 3 d before and during each study day.

The study was conducted according to the Declaration of Helsinki 2008. The study protocol was approved by the Ethics Committee of the University of Bonn (no. 185/10). Written informed consent was obtained from all participants prior to enrolment.

Blood and urine sampling. Blood samples (7.5 mL each) were collected in heparinized tubes (S-Monovette) before (baseline) and 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, and 24 h after L-theanine intake. These intervals were chosen, because the maximum plasma concentration of L-theanine in rats occurred 0.5–1.0 h after L-theanine administration (8,15) and L-theanine was still detectable after 16 h (8,9,15). Blood samples collected before and within 3 h postconsumption were obtained by an indwelling cannula. The 24-h sample was collected by venipuncture. After blood withdrawal, tubes were immediately placed on ice.

Blood was centrifuged at 3000 × g for 20 min at 4°C to obtain plasma and erythrocytes. Erythrocytes were washed twice with 5 mL cold EDTA solution (5 mmol/L), mixed gently, centrifuged at 3000 × g for 20 min at 4°C, and stored at −80°C for at least 15 min. After thawing, erythrocyte lysate was obtained and 300 μL was deproteinized by adding an equal volume of 6% sulfosalicylic acid. Plasma (1 mL) was deproteinized by the addition of 100 μL 30% sulfosalicylic acid. After centrifugation (3000 × g, 20 min, 4°C), 20 μL of the supernatant obtained from plasma and erythrocytes was removed and stored at −80°C until analysis (see below).

Spontaneous urine samples were obtained before the bolus intake to check for L-theanine and ethylamine, which should have been absent if dietary restrictions were maintained. The 24-h urine was collected in 2 intervals (0–3 and 3–24 h, stored at 4°C) after L-theanine intake. Immediately after receiving the urine samples, the volume of each sample was recorded and an aliquot (1 mL) was deproteinized as described for plasma. The supernatant was removed and stored at −80°C until analysis (see below).

Test products. Capsules with pure L-theanine (Suntheanine) were purchased from Taiyo Europe. According to the manufacturers, each capsule provided 100 mg L-theanine, which concurs the results of own investigations (**Table 1**).

For the preparation of green tea, dried tea leaves (Lung Ching, no. 520, TeeGschwendner) were crushed to a 1.4-mm diameter (Rotor Beater Mill SR-100, Retsch) to increase the extraction of L-theanine. On each study day, 7 g of the crushed tea leaves were brewed with 250 mL boiling water for 10 min. The amounts of L-theanine, proteinogenic amino acids, and ethylamine ingested via one capsule or 250 mL green tea are summarized in Table 1.

Analysis of L-theanine, proteinogenic amino acids, and of ethylamine. The concentrations of L-theanine, the proteinogenic amino acids (alanine, asparagine, aspartic acid, arginine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, phenylalanine, serine, threonine, tryptophan, tyrosine, and valine), and ethylamine in all samples were analyzed by Reversed Phase-HPLC (Shimadzu RF-10 AXL) following precolumn derivatization with o-phthalaldehyde as previously described (16).

The limit of detection (LOD)[10] for the proteinogenic amino acids was 0.8 pmol/L (16). The LOD and the limit of quantification for L-theanine and ethylamine were calculated according to the derivation of the German Research Foundation (17). The LOD was 0.01 μmol/L for L-theanine and 0.08 μmol/L for ethylamine (signal to noise ratio = 2.5:1). The corresponding limit of quantifications were 0.02 and 0.12 μmol/L, respectively. The standard curve of L-theanine and ethylamine was linear between 0.005 and 50 μmol/L ($r > 0.95$). Inter- and intra-assay variances were <5%.

Kinetic analysis. Each plasma concentration time curve of L-theanine was fitted using a 1-compartment model with first-order absorption and elimination. A lag time (t_{lag}) was included in this model to account for the delay between L-theanine intake and its appearance in blood (13,18). For this, the following equation was applied:

$$c_t = \frac{a \times k_1}{k_1 - k_2}\left(e^{-k_2 \times (t - t_{lag})} - e^{-k_1 \times (t - t_{lag})}\right),$$

where c_t is the plasma concentration of L-theanine at time t (μmol/L), a is the fraction of L-theanine reaching the systemic circulation depending on the given dose of L-theanine (D) and the hypothetical distribution volume (V_{hyp}) over absolute bioavailability (F): $a = D \times F \times V_{hyp}^{-1}$ (μmol/L); k_1 the absorption rate (per minute), k_2 the elimination rate (per minute), t the time (minutes), and t_{lag} the lag time (minutes). Nonlinear regression was performed with SPSS (Sequential Quadratic Programming, version 19) to estimate the model parameters a, k_1, k_2, and t_{lag} (18). The SD of a, k_1, k_2, and t_{lag} were estimated by using the option "Bootstrap Estimates" in SPSS.

Based on these model parameters, kinetic parameters were calculated: the area under the plasma concentration-time curve corrected to a body weight of 70 kg [AUC$_{70}$; μmol/L × h], maximum plasma concentration corrected to a body weight of 70 kg ($C_{max,70}$; μmol/L), time to reach $C_{max,70}$ after L-theanine intake (t_{max}; min), absorption half-life time (hours), elimination half-life time (hours), and the V_{hyp} (liters). The SDs of the kinetic variables were calculated by using the covariance matrix (18) obtained by the correlations and the SDs of a, k_1, k_2, and t_{lag}. For determining the overall means of the kinetic variables, individual values were weighted to account for heterogeneity in the variances

---

[10] Abbreviations used: AUC$_{70}$, area under the concentration-time curve corrected to a body weight of 70 kg; $C_{max,70}$, maximum plasma concentration corrected to a body weight of 70 kg; k_1, absorption rate; k_2, elimination rate; LOD, limit of detection; t_{lag}, lag time; t_{max}, time to reach $C_{max,70}$ after L-theanine intake; V_{hyp}, hypothetical distribution volume.

TABLE 1 Amounts of L-theanine, proteinogenic amino acids, and ethylamine in one capsule or 250 mL green tea[1,2]

	Capsule	Green tea
n	10	7
L-Theanine, *mg*	101 ± 8.7	103 ± 4.3
Proteinogenic amino acids, *mg*		
Alanine	n.d.	3.8 ± 0.2
Asparagine	n.d.	4.1 ± 0.1
Aspartic acid	n.d.	19.2 ± 0.9
Arginine	n.d.	7.4 ± 0.1
Glutamic acid	n.d.	17.8 ± 0.9
Glutamine	n.d.	24.3 ± 0.5
Glycine	n.d.	0.7 ± 0.1
Isoleucine	n.d.	1.1 ± 0.1
Leucine	n.d.	2.0 ± 0.3
Lysine	n.d.	0.9 ± 0.1
Phenylalanine	n.d.	2.5 ± 0.1
Serine	n.d.	5.3 ± 0.4
Threonine	n.d.	3.5 ± 0.2
Tryptophan	n.d.	1.2 ± 0.1
Tyrosine	n.d.	1.7 ± 0.3
Valine	n.d.	1.7 ± 0.1
Ethylamine, *mg*	n.d.	2.7 ± 0.3

[1] Data are mean ± SD. LOD, limit of detection, n.d., not detectable.
[2] LOD for proteinogenic amino acids, 0.8 pmol/L; LOD for ethylamine, 0.08 μmol/L.

($W_i = \sigma_i^{-2}$), where the weight W_i is inversely proportional to the variance σ_i^2 (18). Results are presented as weighted mean ± SEM.

For ethylamine and glutamic acid in plasma and all substances in erythrocytes, $C_{max,70}$ and t_{max} were determined by visual inspection of individual concentration-time curves. AUC_{70} was calculated according to the trapezoidal rule and subsequent correction to a body weight of 70 kg. Glutamic acid concentrations in plasma and erythrocytes measured after intervention were corrected for baseline values by subtraction. Results are presented as mean ± SD if not otherwise indicated.

Statistical analysis. Metric data were checked for normal distribution and were log-transformed if necessary (concentrations of ethylamine in plasma and L-theanine in erythrocytes). The effects of time, treatment, and their interaction (time × treatment) on the concentration of amino acids and ethylamine in plasma and erythrocytes were investigated by ANOVA followed by a post hoc Tukey test for the comparisons of time points. Kinetic parameters and urinary excretion of amino acids and ethylamine determined after capsule and tea intake were compared using a paired *t* test. If the test of normality failed, Wilcoxon's Signed Rank test was applied instead. For analyzing dose-dependent effects, the AUC_{70} of L-theanine in plasma after intake of 50, 100, and 200 mg L-theanine were compared by ANOVA followed by a post hoc Tukey test. Differences were considered significant at $P < 0.05$. Statistical analysis was performed using SPSS.

Results

All participants completed the study. According to the food records, compliance with dietary restrictions was excellent (data not shown). Consequently, L-theanine and ethylamine were not detectable in the plasma, erythrocytes, and urine of fasting participants.

Plasma and erythrocytes. In plasma, the L-theanine concentration increased time dependently up to 3.0 h postconsumption (for each comparison, $P < 0.001$) and returned to baseline 24 h after intake. Plasma concentration-time curves of L-theanine

were modeled for each participant (**Fig. 1** is a representative one) with good predictions for kinetic parameters (**Table 2**).

The AUC_{70} of L-theanine in plasma increased dose dependently from 50 mg [35.5 ± 10.7 μmol/L × h; $n = 3$] to 100 mg [65.4 ± 17.6 μmol/L × h; $n = 3$] and to 200 mg L-theanine [173 ± 23.0 μmol/L × h; $n = 3$], because the AUC_{70} after the intake of each dose differed from the others ($P < 0.05$) (**Supplemental Fig. 1**).

The glutamic acid concentration in the plasma of fasting participants was 20.7 ± 6.2 μmol/L. After intake of 100 mg L-theanine, the ethylamine and glutamic acid concentrations in plasma increased (**Fig. 2**). Other proteinogenic amino acids in plasma were not affected by time. For all amino acids, including L-theanine, effects by the kind of treatment and time × treatment were not observed. The plasma kinetics of L-theanine, ethylamine, and glutamic acid were comparable after both treatments (Table 2).

In erythrocytes, the L-theanine concentration increased after intake of 100 mg L-theanine compared with baseline (**Supplemental Fig. 2**) and the AUC_{70}, $C_{max,70}$, and t_{max} were comparable after intake of capsules and tea (Table 2). Proteinogenic amino acids did not change and ethylamine could not be detected in erythrocytes.

Urine. Because 2 participants did not collect their urine, data on urinary variables were based on the samples obtained from 10 participants. As expected, glutamic acid was already detectable at baseline (1.2 ± 0.7 μmol/L) in contrast to L-theanine and ethylamine. After intake, L-theanine, ethylamine, and glutamic
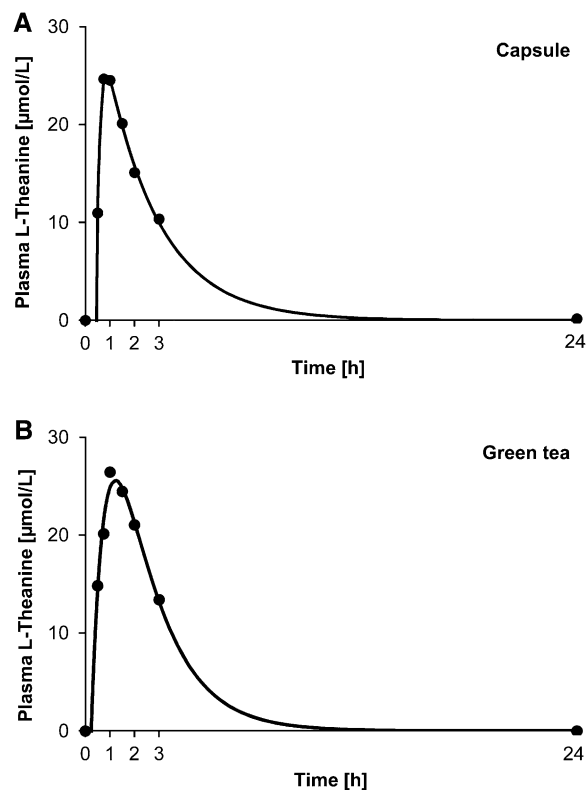
FIGURE 1 Typical concentration-time curve of plasma L-theanine of one participant after intake of 100 mg L-theanine via one capsule (*A*) or 250 mL green tea (*B*). Circles represent measured concentrations of L-theanine. The line represents the modeled plasma concentration-time curve by the use of the 1-compartment model. The t_{lag} was 20 min for capsule and 12 min for green tea, respectively. t_{lag}, lag time.

Kinetics of L-theanine uptake and metabolism   2093

TABLE 2 Kinetic parameters of L-theanine, ethylamine, and glutamic acid in plasma and erythrocytes in healthy participants after a bolus intake of 100 mg L-theanine via one capsule or 250 mL green tea[1,2]

	Plasma		Erythrocytes	
	Capsule	Green tea	Capsule	Green tea
L-Theanine				
AUC_{70}, $\mu mol/L \times h$	57.1 ± 3.6	56.2 ± 2.2	50.5 ± 31.6	62.8 ± 28.6
$C_{max,70}$, $\mu mol/L$	24.3 ± 5.7	26.5 ± 5.2	2.8 ± 1.5	3.5 ± 1.4
t_{max}, h	0.8 ± 0.02	0.8 ± 0.01	7.2 ± 10.2	7.7 ± 9.8
$t_{1/2,a}$, h	0.3 ± 0.01	0.2 ± 0.01		
$t_{1/2,e}$, h	1.2 ± 0.03	0.8 ± 0.01		
V_{hyp}, L	17.1 ± 0.6	15.8 ± 0.6		
Ethylamine				
AUC_{70}, $\mu mol/L \times h$	101 ± 75.1	109 ± 83.7	n.d.	n.d.
$C_{max,70}$, $\mu mol/L$	6.1 ± 3.7	8.2 ± 4.2	n.d.	n.d.
t_{max}, h	5.4 ± 8.7	5.2 ± 8.8	n.d.	n.d.
Glutamic acid				
AUC_{70}, $\mu mol/L \times h$	38.9 ± 13.6	41.7 ± 16.5	276 ± 26.2	261 ± 30.8
$C_{max,70}$, $\mu mol/L$	12.9 ± 9.1	13.1 ± 4.1	43.1 ± 12.2	37.8 ± 19.4
t_{max}, h	1.3 ± 0.4	1.6 ± 0.2	7.5 ± 5.6	7.1 ± 3.2

[1] Data are weighted mean ± SEM, $n = 12$, for L-theanine in plasma calculated by using a 1-compartment model. Individual lag time was ~10–24 min. AUC_{70}, area under the plasma concentration-time curve corrected to a body weight of 70 kg; $C_{max,70}$, maximum plasma concentration corrected to a body weight of 70 kg; n.d., not detectable (concentrations < 0.08 $\mu mol/L$); t_{max}, time to reach $C_{max,70}$ after L-theanine intake; $t_{1/2,a}$, absorption half-life time; $t_{1/2,e}$, elimination half-life time; V_{hyp}, hypothetical distribution volume.
[2] Data are mean ± SD, $n = 12$, for glutamic acid and ethylamine in plasma and all substances in erythrocytes. AUC_{70} was calculated by the trapezoidal rule.

acid were excreted within 3 h and up to 24 h postconsumption. The total amount of L-theanine excreted within 24 h after intake of both capsules (17.3 μmol) and tea (14.2 μmol) corresponded to 3.1 and 2.4% of ingested L-theanine (100 mg $\approx$ 575 μmol), respectively. The excretions of L-theanine, ethylamine, and glutamic acid were comparable after both treatments (**Table 3**).

Discussion

To the best of our knowledge, this is the first study to investigate both the kinetics of L-theanine uptake and its metabolites, ethylamine and glutamic acid, in healthy participants.

Our randomized crossover trial shows that a bolus intake of L-theanine via capsules or green tea increased the plasma concentration of L-theanine (Fig. 1) with comparable kinetics after both treatments (Table 2). This observation is in line with data collected in parallel to our study by van der Pijl et al. (13) after intake of L-theanine via an aqueous solution or black tea. Thus, it is rather unlikely that additional ingredients in tea, e.g., specific proteinogenic amino acids (Table 1), compete with L-theanine for intestinal absorption. For all participants, L-theanine was predicted to be absorbed after a t_{lag} of 10–24 min, leading to a $C_{max,70}$ of ~24–26 $\mu mol/L$. It can be assumed that L-theanine is not only distributed in plasma but also in other tissues with regard to the V_{hyp} of 16–17 L (Table 2). Our study suggests that L-theanine is metabolized to ethylamine and glutamic acid, because their concentrations in plasma increased (Fig. 2) and both were excreted by urine (Table 3) after capsule and tea intake. This is a new finding, because data on the metabolic fate of L-theanine from human studies have not been available yet. In rats, ethylamine and glutamic acids increased dose dependently in plasma and urine after oral and i.g. intake of L-theanine (8,15). In vitro, increasing amounts of ethylamine and glutamic acid were observed after incubation of L-theanine

with either glutaminase or γ-glutamyltranspeptidase (19). Moreover, incubation of L-theanine with homogenate from rats' kidney, but not from rats' small intestine, liver, and brain, increased the concentration of ethylamine and glutamic acid (8,20). Thus, L-theanine may be hydrolyzed to ethylamine and glutamic acid in vivo. This assumption is supported by our observation that only 2.4–3.1% of ingested L-theanine was excreted by urine in contrast to the relatively high excretion of ethylamine and glutamic acid (Table 3). This corresponds to the observation in rats, where only 2.1% of the orally ingested L-theanine (100 mg) was excreted (8). However, in contrast to ethylamine, the amounts of glutamic acid observed in vivo cannot be completely ascribed to orally ingested L-theanine, because glutamic acid is continuously formed in amino acid metabolism by glutaminase, glutamate dehydrogenase, and the transamination of 2-oxoglutarate (21).

Considering that L-theanine is metabolized to equimolar amounts of ethylamine in vitro (19), the mean excretion of 272 and 308 μmol ethylamine within 24 h after intake of capsules and tea, respectively (Table 3), corresponds to 47 and 54% of ingested L-theanine (575 μmol). However, bioavailability of L-theanine is probably higher than 47–54%, because L-theanine also increased in erythrocytes (Supplemental Fig. 2). Because L-theanine in erythrocytes was still detectable 24 h after treatments, a part of L-theanine may be retained in cells. If we consider the $C_{max,70}$ and V_{hyp} of L-theanine in plasma, calculated by the use of the 1-compartment model (Table 2), 72 and 74% of ingested L-theanine should reach the organism after intake of capsules and green tea, respectively.

Our results allow a good prediction of the kinetics of L-theanine uptake in healthy participants. The given dose of 100 mg L-theanine is physiological, because it can be ingested by 4 cups (~500 mL) of green tea (4) or by a single portion of functional drinks. It should be mentioned that our analytical method does not distinguish between L- and D-theanine.
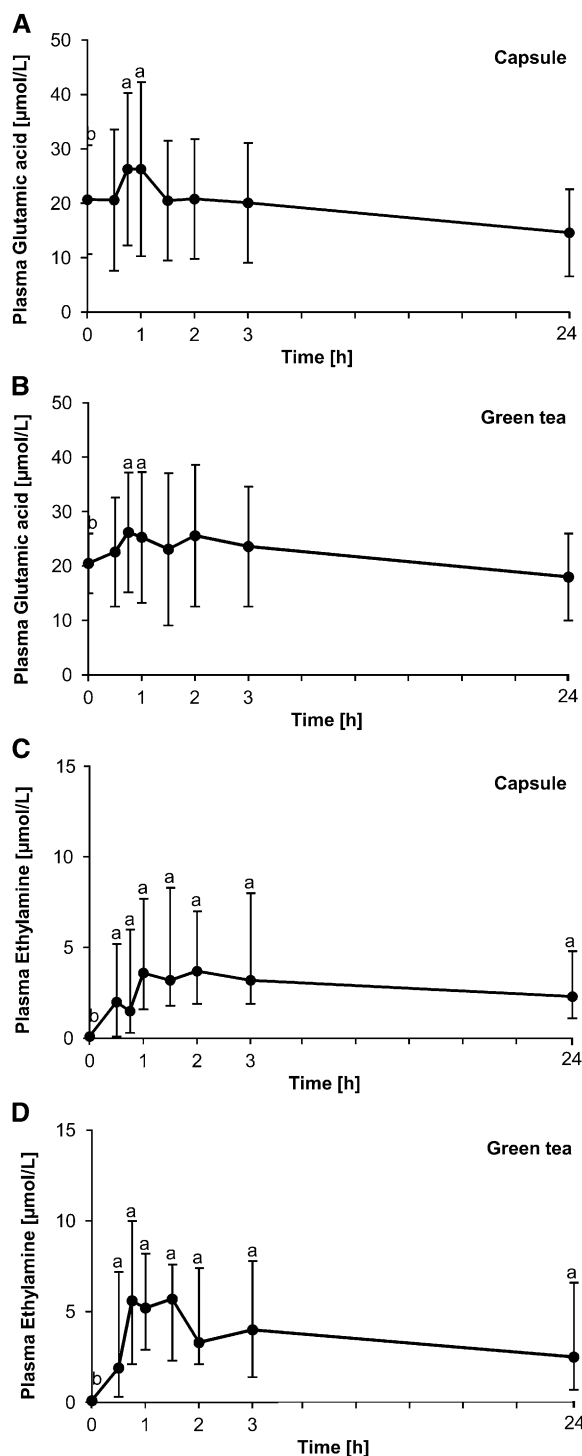
FIGURE 2 Mean concentrations of glutamic acid (*A,B*) and median concentrations of ethylamine (*C,D*) in plasma of healthy participants after a bolus intake of 100 mg L-theanine via one capsule (*A,C*) or 250 mL green tea (*B,D*). Data are mean ± SD, *n* = 12, for glutamic acid and median [IQR] (*n* = 12) for ethylamine, respectively. Time points without a common letter differ, *P* < 0.05.

However, because green tea delivers 98.2% L-theanine (22) and Suntheanine capsules contain even pure L-theanine, the lack of differentiation between enantiomers is not relevant for our results.

We observed a relatively high inter-individual variability in the plasma concentration-time curves of L-theanine and, in particular, of ethylamine and glutamic acid, despite data correction

TABLE 3 Urinary excretion of L-theanine, ethylamine, and glutamic acid in healthy participants after a bolus intake of 100 mg L-theanine via one capsule or 250 mL green tea[1]

	Capsule		Green tea	
	0–3 h	3–24 h	0–3 h	3–24 h
	μmol			
L-Theanine	9.5 (2.2, 13.2)	7.8 (4.8, 17.9)	7.1 (2.8, 15.1)	7.2 (4.1, 14.4)
Ethylamine	92.9 (39.5, 143)	179 (62.5, 261)	101 (48.5, 127)	207 (123, 334)
Glutamic acid	2.6 (1.5, 3.5)	21.3 (16.8, 35.1)	2.2 (1.1, 3.8)	24.8 (11.5, 28.5)

[1] Data are median (IQR), *n* = 10.

to a body weight of 70 kg. Because our participants were comparable in age, BMI, and health status, this variability may be attributed to inter-individual differences in absorption, metabolism, and excretion. To obtain a complete picture of metabolism, L-theanine and its potential metabolites have to be analyzed in different organs after providing labeled L-theanine. In human trials, however, invasive measures beyond blood sampling are nearly impossible. Nevertheless, our results in addition to those obtained in rats provide valuable hints about the metabolic fate of L-theanine.

In conclusion, L-theanine is rapidly absorbed in healthy participants after intake of capsules and green tea. The major part of L-theanine seems to be hydrolyzed to ethylamine and glutamic acid, which are excreted by urine. A minor part is retained in erythrocytes. The kinetics and urinary excretion of L-theanine, ethylamine, and glutamic acid are comparable after intake of capsules and green tea. Thus, functional effects of L-theanine intake may result from L-theanine, ethylamine, or glutamic acid. Because glutamic acid is converted to glutamine, future studies should investigate if L-theanine may be an alternative source of glutamine, which is essential for critically ill patients.

Literature Cited
1. Sakato Y. The chemical constituents of tea. A new amide, theanine. Nippon Nogei Kagaku Kaishi (Tokyo). 1950;23:262–7.
2. Casimir J, Jadot J, Renard M. Separation and characterization of N-ethyl-gamma-glutamine from Xerocomus badius. Biochim Biophys Acta. 1960;39:462–8.
3. Chen CN, Liang CM, Lai JR, Tsay JS, Lin JK. Capillary electrophoretic determination of theanine, caffeine, and catechins in fresh tea leaves and oolong tea and their effects on rat neurosphere adhesion and migration. J Agric Food Chem. 2003;51:7495–503.
4. Hänsel R, Keller K, Rimpler H, Schneider G. Hager's handbook of pharmaceutical practise for druggits. 4th ed. Heidelberg (Germany): Springer-Verlag; 1992. p. 628–40.
5. Weisburger JH. Tea and health: a historical perspective. Cancer Lett. 1997;114:315–7.

6. Nathan PJ, Lu K, Gray M, Oliver C. The neuropharmacology of L-theanine(N-ethyl-L-glutamine): a possible neuroprotective and cognitive enhancing agent. J Herb Pharmacother. 2006;6:21–30.

7. Vuong QV, Bowyer MC, Roach PD. L-theanine: properties, synthesis and isolation from tea. J Sci Food Agric. 2011;91:1931–9.

8. Unno T, Suzuki Y, Kakuda T, Hayakawa T, Tsuge H. Metabolism of theanine, gamma-glutamylethylamide, in rats. J Agric Food Chem. 1999;47:1593–6.

9. Terashima T, Takido J, Yokogoshi H. Time-dependent changes of amino acids in the serum, liver, brain and urine of rats administered with theanine. Biosci Biotechnol Biochem. 1999;63:615–8.

10. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. J Clin Psychiatry. 2010;71:839–54.

11. Bryan J. Psychological effects of dietary components of tea: caffeine and L-theanine. Nutr Rev. 2008;66:82–90.

12. Ritsner MS, Miodownik C, Ratner Y, Shleifer T, Mar M, Pintov L, Lerner V. L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: an 8-week, randomized, double-blind, placebo-controlled, 2-center study. J Clin Psychiatry. 2011;72:34–42.

13. van der Pijl PC, Chen L, Mulder TPJ. Human disposition of L-theanine in tea or aqueous solution. J Funct Food. 2010;2:239–44.

14. WHO. Report of a WHO consultation on obesity, 2000. In: Obesity: preventing and managing the global epidemic. Geneva: WHO; 2000.

15. Desai MJ, Gill MS, Hsu WH, Armstrong DW. Pharmacokinetics of theanine enantiomers in rats. Chirality. 2005;17:154–62.

16. Fürst P, Pollack L, Graser TA, Godel H, Stehle P. Appraisal of four pre-column derivatization methods for the high-performance liquid chromatographic determination of free amino acids in biological materials. J Chromatogr. 1990;499:557–69.

17. Frehse H, Thier HP. The limits of detection an determination in residue analyses: their derivation according to the new DFG-Approach. GIT Fachz Lab. 1991;35:285–91.

18. Gabrielsson J, Weiner D. Pharmacokinetic and pharmacodynamic data analysis: concepts and applications. Stockholm: Swedish Pharmaceutical Press; 2000. p. 27–69.

19. Sadzuka Y, Sugiyama T, Nagamine M, Umegaki K, Sonobe T. Efficacy of theanine is connected with theanine metabolism by any enzyme, not only drug metabolizing enzymes. Food Chem Toxicol. 2006;44:286–92.

20. Tsuge H, Sano S, Hayakawa T, Kakuda T, Unno T. Theanine, gamma-glutamylethylamide, is metabolized by renal phosphate-independent glutaminase. Biochim Biophys Acta. 2003;1620:47–53.

21. Nedergaard M, Takano T, Hansen AJ. Beyond the role of glutamate as a neurotransmitter. Nat Rev Neurosci. 2002;3:748–55.

22. Desai MJ, Armstrong DW. Analysis of derivatized and underivatized theanine enantiomers by high-performance liquid chromatography/ atmospheric pressure ionization-mass spectrometry. Rapid Commun Mass Spectrom. 2004;18:251–6.