Kinetics of L-Theanine Uptake and Metabolism in Healthy Participants Are Comparable After Ingestion of L-Theanine via Capsules and Green Tea¹–⁴

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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. doi: 10.3945/jn.112.166371.

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 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 t-theanine in the plasma of healthy men after an intake of 25, 50, and 200 mg t-theanine provided via an aqueous solution or black tea.

However, data on the metabolic fate of t-theanine from human studies are lacking. Thus, the present study investigated the kinetics of t-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. t-Theanine, proteinogenic amino acids, and ethylamine were obtained from Sigma-Aldrich, acetoni-trile 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/m² (range: 18.5 and 24.9 kg/m² (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 t-theanine, either in isolated form via capsules or via 250 mL green tea, after a 12-h overnight fast. On further study day, 7 g of the crushed tea leaves were brewed with 250 mL boiling water for 10 min. The amounts of t-theanine, proteinogenic amino acids, and ethylamine ingested via one capsule or 250 mL green tea are summarized in Table 1.

Analysis of t-theanine, proteinogenic amino acids, and of ethylamine. The concentrations of t-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 t-theanine and ethylamine were calculated according to the derivation of the German Research Foundation (17). The LOD was 0.01 μmol/L for t-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 t-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 t-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 t-theanine intake and its appearance in blood (13,18). For this, the following equation was applied:

\[ c_t = \frac{a}{1 + \left( e^{-k_2 t} \cdot C_{t_{lag}} \right) - e^{-k_1 t} \cdot C_{t_{lag}}}, \]

where \( C_t \) is the plasma concentration of t-theanine at time \( t (\mumol/L) \), \( a \) is the fraction of t-theanine reaching the systemic circulation depending on the given dose of t-theanine (D) and the hypothetical distribution volume (\( V_{hyp} \)) over absolute bioavailability (\( F \); \( a = D \times V_{hyp} \times F \times V_{hyp}^{-1} \)), \( k_1 \) 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 \( t_{lag} \). 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 t-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 (W = 1/σ^2).

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 t-theanine intake; V_{hyp}, hypothetical distribution volume.
where the weight \( W_i \) is inversely proportional to the variance \( \sigma_i^2 \) (18). Results are presented as weighted mean \( \pm \) SEM.

For ethylamine and glutamic acid in plasma and all substances in erythrocytes, \( C_{\text{max},70} \) and \( t_{\text{max}} \) 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 \( \pm \) 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 \( \times \) 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 mg \([35.5 \pm 10.7 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\) to 100 mg \([65.4 \pm 17.6 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\) and to 200 mg \( l \)-theanine \([173 \pm 23.0 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\), 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 \( 20.7 \pm 6.2 \mu\text{mol}/\text{L} \). 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 \( \times \) 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\(_{70}\), \( C_{\text{max},70} \), and \( t_{\text{max}} \) 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 \((1.2 \pm 0.7 \mu\text{mol}/\text{L})\) in contrast to \( l \)-theanine and ethylamine. After intake, \( l \)-theanine, ethylamine, and glutamic acid 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 \([35.5 \pm 10.7 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\) to 100 mg \([65.4 \pm 17.6 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\) and to 200 mg \( l \)-theanine \([173 \pm 23.0 \mu\text{mol}/(\text{L} \cdot \text{h}); \ n = 3]\), because the AUC\(_{70}\) after the intake of each dose differed from the others \( (P < 0.05) \) (Supplemental Fig. 1).

**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).

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suggests that L-theanine is metabolized to ethylamine and specific proteinogenic amino acids (Table 1), compete with Thus, it is rather unlikely that additional ingredients in tea, e.g.,
dose dependently in plasma and urine after oral and i.g. intake of
available yet. In rats, ethylamine and glutamic acids increased
to 3.1 and 2.4% of ingested L-theanine (100 mg
of both capsules (17.3
m
38
mol) and tea (14.2
mol) corresponded to 3.1 and 2.4% of ingested L-theanine (100 mg ≈ 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. Moreover, incubation of L-theanine with homogenate from tissues with regard to the metabolism of L-theanine is probably higher than 47–54%, because 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 Cmax,70 and Vhypo 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.

### 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

<table>
<thead>
<tr>
<th>L-Theanine</th>
<th>Plasm</th>
<th>Green tea</th>
<th>Erythrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Capsule</td>
<td>Green tea</td>
<td>Capsule</td>
</tr>
<tr>
<td>AUCmax,70, µmol/(L·h)</td>
<td>57.1 ± 3.6</td>
<td>56.2 ± 2.2</td>
<td>50.5 ± 3.16</td>
</tr>
<tr>
<td>Cmax,70, µmol/L</td>
<td>24.3 ± 5.7</td>
<td>26.5 ± 5.2</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>tmax, h</td>
<td>0.8 ± 0.02</td>
<td>0.8 ± 0.01</td>
<td>7.2 ± 10.2</td>
</tr>
<tr>
<td>t1/2,a, h</td>
<td>0.3 ± 0.01</td>
<td>0.2 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>t1/2,e, h</td>
<td>1.2 ± 0.03</td>
<td>0.8 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Vhypo, L</td>
<td>17.1 ± 0.6</td>
<td>15.8 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Ethylamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCmax,70, µmol/(L·h)</td>
<td>101 ± 75.1</td>
<td>109 ± 83.7</td>
<td>n.d.</td>
</tr>
<tr>
<td>Cmax,70, µmol/L</td>
<td>6.1 ± 3.7</td>
<td>8.2 ± 4.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>tmax, h</td>
<td>5.4 ± 8.7</td>
<td>5.2 ± 8.8</td>
<td>n.d.</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCmax,70, µmol/(L·h)</td>
<td>38.9 ± 13.6</td>
<td>41.7 ± 16.5</td>
<td>276 ± 26.2</td>
</tr>
<tr>
<td>Cmax,70, µmol/L</td>
<td>12.9 ± 9.1</td>
<td>13.1 ± 4.1</td>
<td>43.1 ± 12.2</td>
</tr>
<tr>
<td>tmax, h</td>
<td>1.3 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>7.5 ± 5.6</td>
</tr>
</tbody>
</table>

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. AUCmax, area under the plasma concentration-time curve corrected to a body weight of 70 kg; Cmax,70, maximum plasma concentration corrected to a body weight of 70 kg; n.d., not detectable (concentrations < 0.08 µmol/L); tmax, time to reach Cmax,70 after L-theanine intake; t1/2,a, absorption half-life time; t1/2,e, elimination half-life time; Vhypo, hypothetical distribution volume.

2 Data are mean ± SD, n = 12, for glutamic acid and ethylamine in plasma and all substances in erythrocytes. AUCmax was calculated by the trapezoidal rule.
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 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.

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**Literature Cited**