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Theogallin and L-theanine as active ingredients in decaffeinated green tea extract: II. Characterization in the freely moving rat by means of quantitative field potential analysis

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Abstract

The model Tele-Stereo-EEG (continuous recording of intracerebral field potentials in the freely moving rat to produce an electropharmacogram) has been used to see if L-theanine- and theogallin-enriched decaffeinated green tea extract would change electrical brain activity after oral administration, to provide proof of access of active components to the brain via the blood–brain barrier. Baseline recording (45 min) was followed by a 5-h recording session after oral ingestion of the extract or single components: L-theanine, theogallin and quinic acid, a suggested metabolite of theogallin. Power spectra from Fast Fourier Transformed (FFT) field potential changes were divided into six frequency bands (delta, theta, alpha1, alpha2, beta1 and beta2). No effects could be measured using a saline solution for control purposes. Oral administration of 75 mg kg^{-1} total extract led to power decreases mainly in delta and alpha2 frequencies during the first hour. This pattern has been observed in the presence of stimulatory synthetic compounds. Oral administration of 30 mg kg^{-1} L-theanine led to power decreases of nearly all frequencies, being more pronounced during the second and following hours in comparison with the first hour. Ingestion of 20 mg kg^{-1} theogallin also showed a power decreasing effect on cortical activity. Its possible metabolite quinic acid (10 mg kg^{-1}, p.o.) also produced decreases in delta, alpha2 and beta1 frequencies. Measurement of motion resulted in an increase during the first hour in the presence of theogallin and L-theanine. A tendential decrease was observed in the presence of L-theanine during the last hour at its presumably highest plasma levels. The results with the administration of the total extract provided evidence for the maior involvement of L-theanine and theogallin (or its presumable metabolite quinic acid) in its action, since no other active compounds were present in the extract. These compounds could be classified by comparison with reference drugs using discriminant analysis as being antidepressive and cognition enhancing, respectively. The extract appeared among those drugs having stimulatory effects.

Introduction

There is an intimate relationship between neurotransmitter action within a given network of neurons and the electrical features resulting from it. Since neurotransmitters act on the molecular level by activating ion channels, the neuron has to integrate these bombardments of excitatory and inhibitory events, finally leading to a particular type of neuronal firing or to no activity at all (Marder & Prinz 2002). Hence, the electrical activity of a neuronal network provides a high level of integration which is situated in between the biochemical molecular basis of communication and its control of behaviour. It is therefore very meaningful to pick up this electrical activity to create a link between this biochemical base of drug action on a molecular level and the desired drug effects on behaviour. The local electrical network activity in a given place of the depth of the brain is called a field potential leading to the electropharmacogram in the presence of drugs and corresponds to the electroencephalogram (multiple field potentials) as obtained from the scalp in man.

Analysis of these brain field potentials recorded by the Tele-Stereo-EEG method (continuous recording of intracerebral field potentials in the freely moving rat to produce an electropharmacogram) has been proven to be a very sensitive tool to characterize drug

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effects on the central nervous system. Since the first use of this method it has become clear that the electrical power of single frequency ranges, as defined by Dimpfel et al (1986), change independently from each other depending on the particular behavioural or drug condition. After drug administration the pattern of changes of the brain field potential with respect to specially defined frequency ranges is called an electropharmacogram of this drug. Meanwhile electropharmacograms of more than 100 compounds have been obtained, including more than 50 standard drugs (e.g. analgesics, antidepressants, neuroleptics, stimulants, tranquilizers, sedatives and narcotics). In general, electropharmacograms show prominent differences for drugs prescribed for different indications and are similar for drugs with similar clinical use (Dimpfel 2003).

The current experimental series was undertaken to learn more about the effects of a special decaffeinated green tea extract with high amounts of L-theanine and theogallin (Figure 1). It was hoped that the electropharmacograms produced would resemble the results already obtained by the action of known drugs and that in general a difference could be observed to the pattern created by drugs as published earlier (Dimpfel et al 1992).

Materials and Methods

Materials

Extract and fractions tested were diluted in artifical cerebrospinal fluid to give the final concentration as indicated and tested using one dosage. Extract and test samples were supplied by Plantextrakt: enriched green tea extract Lab. 15920096; glutamic acid Lab. 15920366; theogallin 97% pure Lab. 15920398; L-theanine pure Lab. 15920365; quinic acid 98% pure (charge # S28053-485 from Sigma-Aldrich Chemie GmbH, Taufkirchen).

In principle the extract was prepared by water extraction and subsequent removal of caffeine by liquid–liquid extraction. Enrichment of L-theanine and theogallin was performed by column chromatography. The extract was concentrated and spray dried. For the extraction process green tea fannings where used as the starting material. Extraction was performed by maceration with water at 20–60°C as solvent, without stirring. Maceration time was approximately 60–120 min. The liquid green tea extract was processed further by liquid–liquid extraction with water/ethyl acetate to remove the caffeine. The water phase containing the active principles L-theanine and theogallin was subsequently subjected to column chromatography with a column 800-mm high and 150-mm diameter. The adsorption material was divinylbenzene. The first passage of solvent (water) during adsorption was discarded, approximately 1.2 bed volumes. Elution was performed with demineralized water, with approximately 5.3 bed volumes. The first part of the elution was discarded (approximately 1 bed volume). The second part (approximately 4 bed volumes) was collected, containing the L-theanine- and theogallin-enriched extract. The detection was performed at 261 nm with an UV spectroscope to monitor the chromatographic process.

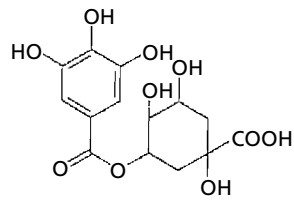
The composition of the extract is outlined in Table 1.

Animal experiments

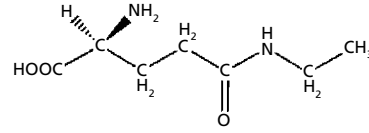
Adult Fisher rats (6-months-old, day–night converted) were implanted with four bipolar concentric steel electrodes within a stereotactic surgical procedure. All four electrodes were placed 3-mm lateral within the left hemisphere. Anterior coordinates were 12.2, 5.7, 9.7 and 3.7 mm for frontal cortex, hippocampus, striatum and reticular formation (according to the atlas of Paxinos & Watson (1982)). A base carrying four bipolar stainless steel semi-micro-electrodes (neurological electrodes "SNF 100" from Rhodes Medical Instruments, Inc., Summerland, CA) and a 5-pin-plug was fixed to the skull by dental cement interacting with three steel screws placed a distance into the bone. The distant recording spot of the electrode was the active electrode whereas the proximal spots of the four electrodes were connected to each other to give a common reference. The base was carrying a plug to receive the transmitter later on (weight 5.2 g including battery, 26 × 12 × 6 mm).

Animals were given two weeks for recovery, after which time the transmitter was plugged in for adaptation and control experiments with saline. During the recording rats were not restricted and could move freely, but food was not available (chewing would have produced too many artefacts). The principles of laboratory animal care were followed in all trials and the local authorities responsible for animal care allowed the performance according to German Health Guidelines. The experimental series had been approved by "Regierungspräsidium Giessen" dated 27th September 2006.

EEG signals were recorded from the frontal cortex, hippocampus, striatum and reticular formation from inside a



Theogallin (3-galloyl-quinic acid)



L-Theanine (N-ethyl-L-glutamine)

Figure 1 The structures of theogallin and L-theanine.

Table 1 The composition of the extract

Water	3.52%
Minerals (ash)	24.01%
Protein (Nx6,25)	20.60%
Amino acids (HPLC, sum)	3.52%
Glutamic acid	1.18%
Fat	0.10%
Polyphenols (Folin)	2.50%
Tea catechins (HPLC, sum)	0.10%
Caffeine (HPLC)	<0.01%
L-Theanine (HPLC)	9.71%
Theogallin (HPLC)	4.65%

room totally shielded in copper. Signals were wirelessly transmitted by a radio-telemetric system (Rhema Labortechnik, Hofheim, Germany, using 40 MHz as carrier frequency) and were amplified and processed as described previously to give power spectra of 0.25 Hz resolution (Dimpfel et al 1986; Dimpfel 2003). In short, after automatic artefact rejection, signals were collected in sweeps of 4-s duration and Fast Fourier transformed using a Hanning window. Sampling frequency was 512 Hz. Four values were averaged to give a final sampling frequency of 128 Hz, well above the Nyquist frequency. The resulting electrical power spectra were divided into six specially defined frequency ranges (delta: 0.8–4.5 Hz; theta: 4.75–6.75 Hz; alpha1: 7.00–9.50 Hz; alpha2: 9.75–12.50 Hz; beta1: 12.75–18.50 Hz; beta2: 18.75–35.00 Hz). These frequency ranges were recognized to change independently from each other in all earlier trials. Spectra were averaged in steps of 3 min each and displayed on-line. In an off-line procedure spectra were averaged to give 30 min or longer periods for further analysis and data presentation.

Each extract, single compound or saline was administered orally as a single dose. After a pre-drug period of 45 min for baseline recording (giving 100%), effects were observed for 300 min. Changes of the recorded electrical power ($\mu V^2/\omega$) were documented in percent of the pre-dose value at 1-h intervals. Values represented the mean of n = 6 animals, except for theogallin (n = 4). Changes within the four brain areas were documented separately. Animals were exposed to one dose per week (leading to a 6-day drug free interval).

Statistical analysis

Statistical analysis was performed according to Ahrens & Läuter (1974) as a multivariate approach, and then univariate for each of the spectral frequencies with respect to each brain area separately.

Results

Vehicle control

Oral administration of saline did not show changes in the EEG power spectrum in comparison with the reference values (Figure 2). Oral administration of up to 10 mg kg^{-1} glutamic acid did not induce any changes of electrical power (data not shown).

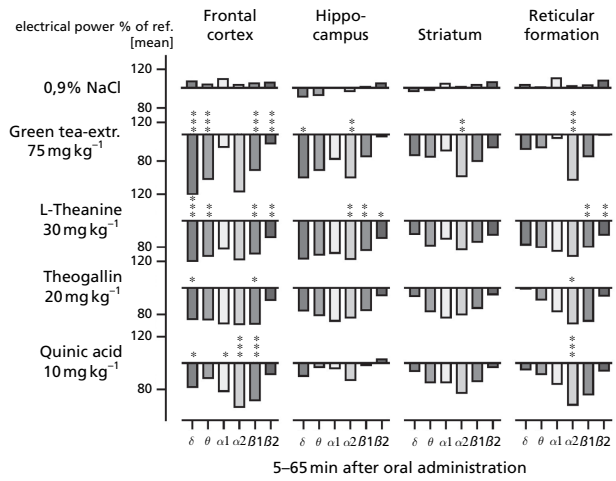


Figure 2 Comparison of the effect of oral administration of the total extract with single constituents for the first hour after administration on the change of spectral power in four brain areas. Frequency ranges of delta, theta, alpha1, alpha2, beta1 and beta2 power are given under Materials and Methods. Data are given as average of n = 6 rats, except for theogallin (n = 4 because of limited material). Multivariate analysis according to Ahrens & Läuter (1974) revealed statistically significant difference in comparison with saline only for green tea extract at $P < 0.10$. Results for the univariate analysis regarding single frequencies are documented as $^*P < 0.1$, $^{**}P < 0.05$, $^{***}P < 0.025$.

Effects of the total decaffeinated extract

Oral administration of 75 mg kg^{-1} green tea extract to six animals resulted in a pattern of changes of spectral power. This was dominated by decreases in delta, alpha2 and, to a lesser extent, beta1, mainly in the frontal cortex and hippocampus. A very stable statistically significant decrease of alpha2 spectral power was seen throughout all brain areas (Figure 2). The statistically significant prominent changes only lasted for the first hour after administration, but after this the basic pattern of changes was seen for the next few hours.

Effects of L-theanine

Oral administration of 30 mg kg^{-1} L-theanine produced decreases in spectral power of nearly all frequencies, dominated by the alpha2 band. Strongest effects were seen within the first hour after ingestion, but changes lasted up to the fifth hour after ingestion. With respect to brain areas, the frontal cortex and hippocampus were mainly involved over time (Figures 2 and 3). During the first hour statistical significances were reached for nearly all frequencies for cortical and hippocampal activity.

Effects of theogallin

Oral administration of 20 mg kg^{-1} theogallin produced changes, but these were less pronounced ($P < 0.1$ for alpha and beta1 spectral power). Nevertheless theogallin at this low dose seemed to act on the brain, but further data are needed for confirmation since the material was too limited to allow more experiments (Figure 2).

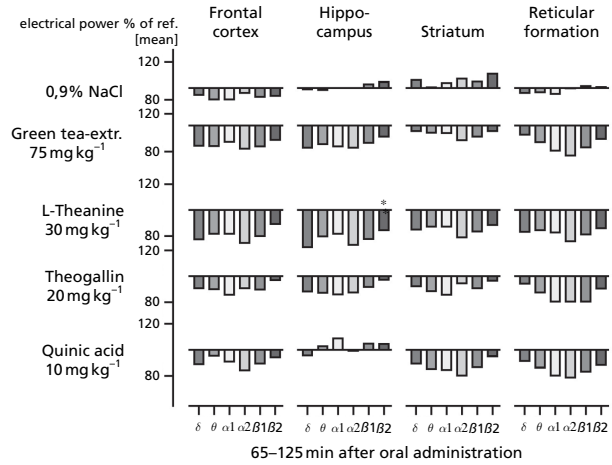


Figure 3 Comparison of the effect of oral administration of the total extract with single constituents for the second hour after administration on the change of spectral power in four brain areas. Frequency ranges of delta, theta, alpha1, alpha2, beta1 and beta2 power are given under Materials and Methods. Data are given as average of n = 6 rats.

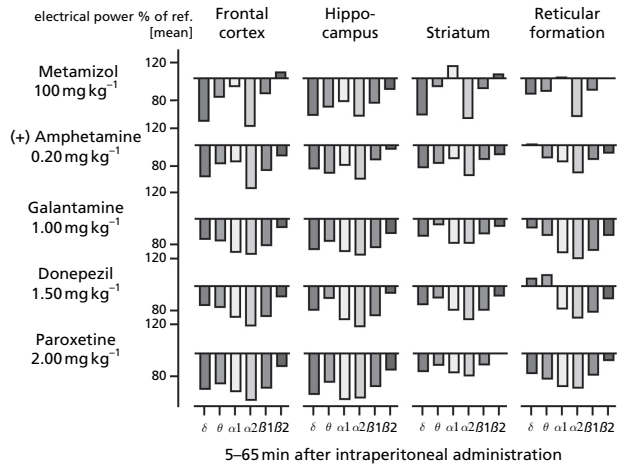


Figure 4 Comparison of the electropharmacogram of green tea and its constituents with those of standard reference drugs from our data base, which showed a similar pattern of changes.

Effects of quinic acid

Oral administration of 10 mg kg^{-1} quinic acid, a possible metabolite of theogallin, resulted in changes of spectral power of field potentials during the first hour of recording after administration. In the frontal cortex mainly delta, alpha2 and beta1 power decreased to a similar degree as seen with the total extract. Changes within the alpha2 and beta1 power were most consistent (Figures 1 and 3) and statistically significant with respect to frontal cortex and reticular formation.

Comparison of single compounds to total extract

The effects of quinic acid and theogallin were similar with respect to the brain regions involved and also with respect to the change of the frequency pattern. A common denominator for the observed effects could be seen in the massive decrease of alpha2 spectral power (Figures 2 and 3).

Comparison with known drug effects

The effects of the whole extract and the single constituents of green tea extract were compared with drug effects from our data base. As can be seen in Figure 4 changes were similar to those observed for the action of antidementive, stimulating and antidepressive/analgesic drugs. A possibility of differentiating drug action statistically with respect to all frequencies and brain areas in total was also provided by discriminant analysis. Having six frequency ranges and four different brain areas the calculations were performed with 24 variables. The results are shown in Figure 5 as a multivariate six-dimensional documentation. Note that in addition to three projection axes (x-, y- and z-axis) representing the first to third discriminant axis, results from the 4^{th} to 6^{th} discriminant function are depicted by using an additive colour mixture of green, red and blue (similar to the technique used in TV-technology). Thus not only the three dimensional projection is used for classification of the electropharmacogram but additionally the type of colour can be used to differentiate drug effects from each other. The analysis of the effect of green tea extract and its main constituents revealed that theanine became located near imipramine and theogallin near paroxetine. Green tea appeared in the neighbourhood of metanicotine. Quinic acid showed up not far away from the antidepressive drugs. In summary, they all grouped together near stimulating and antidementive drugs, such as donepezil or galantamine (Figure 5, Table 2).

Effects on motion

To relate measurements of electrical activity of the brain to behaviour, a newly developed video tracking system was used. This system followed the head movement of the rat during motion. As documented in Table 3 recording of the motion showed a small increase in comparison with the saline control in the presence of theogallin and quinic acid during the first hour after administration and then slowly approached control values. Only L-theanine produced less movement during the last 2 h. Differences were not statistically significant in comparison with saline administration, and thus no relationship to neurophysiological recordings could be seen.

Discussion

After having tested the L-theanine- and theogallin-enriched decaffeinated green tea extract in man, and succeeding in finding neurophysiological effects on the brain of volunteers, the question arose, which of the components of green tea could be responsible for this action? In general, the stimulating action of green tea is attributed to the presence of caffeine. However, the present extract only contained traces of caffeine. Thus, other compounds must have been responsible for the effects. Fractionation of the extract and chemical analysis

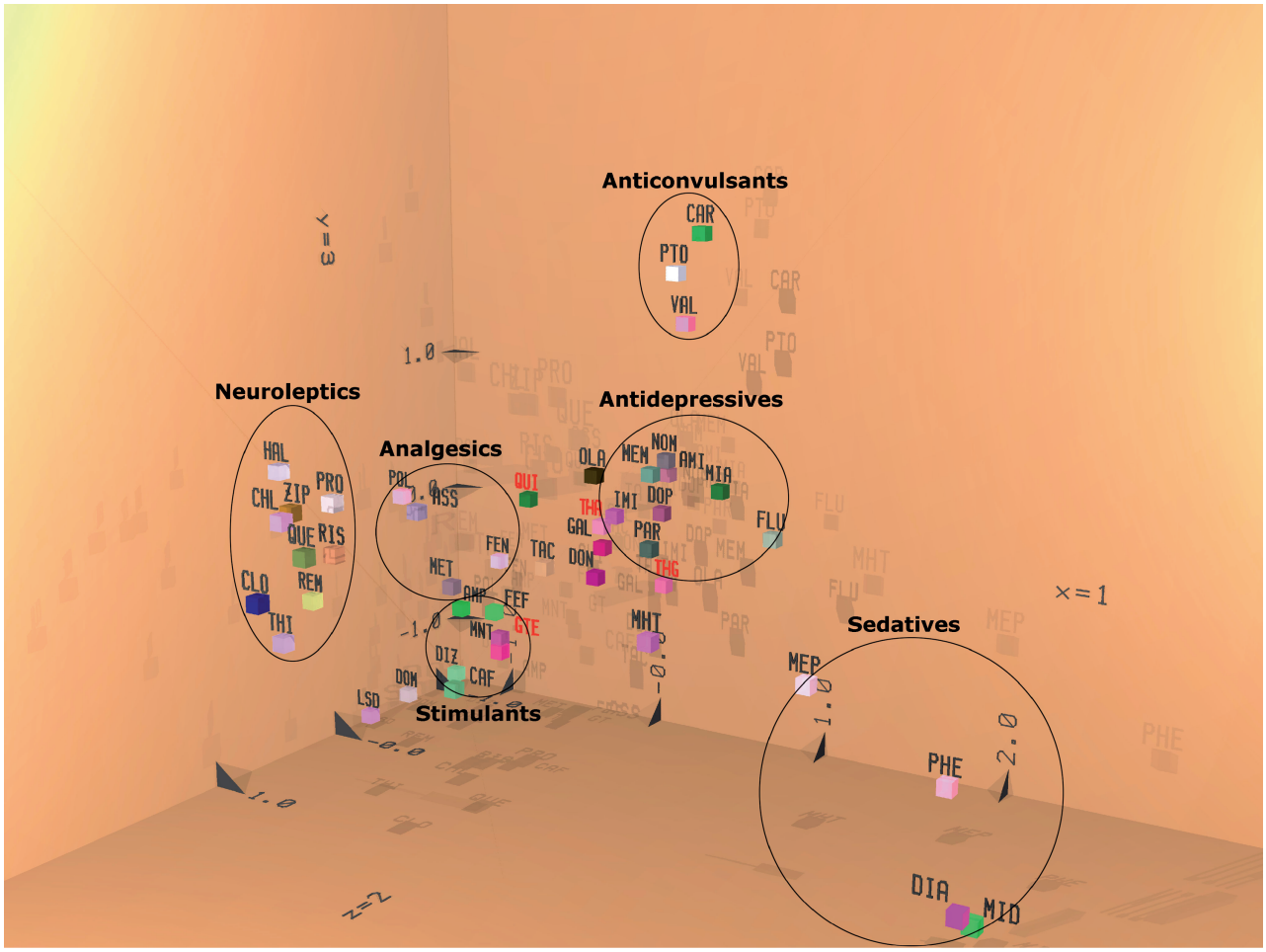


Figure 5 Classification of the electropharmacograms of green tea and its main constituents with regard to clinical indication and comparison with standard reference drugs by discriminant analysis. Projection from polydimensional space with depiction of the results of the first three discriminant axes is depicted on the x-, y- and z-axis. Results from the 4th to 6th discriminant axes are documented by additive colour mixture of red, green and blue. GTE, green tea extract; THA, theanine; THG, theogallin; QUI, quinic acid.

revealed that amino acids made up a considerable part of the mass and that among them L-theanine was enriched (to give approximately 9.7% of the total extract). A compound characteristic to tea, theogallin, was also present in a considerable amount (4.6%). These fractions or components required testing separately to explain the net effect of the total extract as seen in-vitro in the hippocampus slice preparation (Dimpfel et al 2007).

The total extract revealed a strong stimulatory action on field potentials derived from power decreases in delta, theta and alpha frequencies. Time dependent effects could also be observed after oral administration of one dosage of each of the compounds, which roughly corresponded to double the amount present in the total extract (Figures 2 and 3). The main frequencies involved were delta, theta and alpha2. Surprisingly the effect of L-theanine was still present 5 h after administration. This result was in line with metabolism data reported by Unno et al (1999), who reported on peak plasma values 5 h after administration. An action of L-theanine on the brain was also reported by Kakuda et al (2000). With respect to the dose used, L-theanine was administered at double the dose (30 mg kg^{-1}) in comparison with the content within the total extract (9.7%). This was to ensure a reliable effect in the small number of animals studied. Since one of the reasons to perform this study was to compare the effects of the total extract with the effects produced by single chemically-defined constituents a direct comparison of the effects was documented in Figures 2 and 3. Obviously there was some similarity between the effects of theogallin and its possible metabolite quinic acid. The impression could be given that a combination of L-theanine and quinic acid could give a pattern as observed for the administration of the total extract. This impression at least holds for the first hour of recording. Thus, we might assume that L-theanine and theogallin (or in addition its possible metabolite quinic acid) were the major active principles responsible for the stimulating effects of the special tea extract on electrical brain activity, since glutamic acid (10 mg kg^{-1}) had no effect (not shown).

With regard to the specific frequency changes observed, it is known from previous studies that changes in delta activity predominantly occur after treatment of the animals with compounds

Table 2 Listing of abbreviations of drugs tested in the same model with their respective dosages (mg kg^{-1}) and times of recording as depicted in Figure 5 (discriminant analysis showing automatic grouping of drugs with similar clinical indication at roughly equipotent dosages)

Neuroleptics			
RIS	Risperidone	0.25	5–35 min
ZIP	Ziprasidone	1.00	5–35 min
QUE	Quetiapine	2.50	5–35 min
HAL	Haloperidol	0.50	5–35 min
REM	Remoxipride	10.00	5–35 min
CHL	Chlorpromazine	0.50	5–35 min
PRO	Prothipendyl	1.00	5–35 min
CLO	Clozapine	3.00	5–35 min
THI	Thioridazine	5.00	5–35 min
OLA	Olanzapine	3.00	5–35 min
Anticonvulsants			
VAL	Valproic acid	75.00	95–125 min
PTO	Phenytoin	4.00	95–125 min
CAR	Carbamazepine	15.00	95–125 min
Hallucinogenics			
DIZ	Dizocilpine	0.25	5–35 min
LSD	LSD	0.05	5–35 min
DOM	R-DOM	0.20	5–35 min
Sedatives			
MHT	Methohexital	20.00	35–65 min
MEP	Meprobamate	60.00	35–65 min
DIA	Diazepam	0.50	35–65 min
MIA	Midazolam	0.05	35–65 min
PHE	Phenobarbitone	60.00	35–65 min
Analgesics			
ASS	Acetylsalicylic acid	200	5–35 min
MET	Metamizol	100	5–35 min
POL	L-Polamidon	1.00	5–35 min
FEN	Fentanyl	0.075	5–35 min
Stimulants			
CAF	Caffeine	1.00	5–35 min
FEF	Fenfluramine	1.00	5–35 min
MNT	Metanicotine	1.00	5–35 min
AMP	Amphetamine	0.20	5–35 min
Antidementives			
TAC	Tacrine	0.75	5–35 min
GAL	Galantamine	1.00	5–35 min
DON	Donepezil	1.50	5–35 min
DOP	DOPA	2.50	5–35 min
Antidepressives			
PAR	Paroxetine	2.00	5–35 min
MEM	Memantine	3.00	5–35 min
IMI	Imipramine	10.00	5–35 min
MIA	Mianserine	5.00	5–35 min
AMI	Amitriptyline	10.00	5–35 min
FLU	Fluvoxamine	40.00	5–35 min
NOM	Nomifensine	1.00	5–35 min
GTE	Green tea extract	75.00	5–65 min
THG	Theogallin	20.00	5–65 min
THA	L-Theanine	30.00	5–65 min
QUI	Quinic acid	10.00	5–65 min

Table 3 Documentation of motion analysis. Values are given in percent of the pre-drug baseline

Substance	Dose (mg kg^{-1})	Time (min)	Motion (% of ref)
Saline	0	5–65	93.20
L-Theanine	30	5–65	94.13
Theogallin	20	5–65	134.13
Quinic acid	10	5–65	120.62
Saline	0	65–125	96.52
L-Theanine	30	65–125	84.93
Theogallin	20	65–125	127.40
Quinic acid	10	65–125	102.34
Saline	0	125–185	93.24
L-Theanine	30	125–185	83.59
Theogallin	20	125–185	84.43
Quinic acid	10	125–185	106.07
Saline	0	185–245	102.30
L-Theanine	30	185–245	71.06
Theogallin	20	185–245	79.32
Quinic acid	10	185–245	83.58
Saline	0	245–305	92.14
L-Theanine	30	245–305	61.54
Theogallin	20	245–305	59.64
Quinic acid	10	245–305	69.24

No statistical significance could be reached for any of the compounds.

affecting the cholinergic system (Dimpfel 2005). This frequency obviously plays a major role during the action of the green tea extract, especially with respect to the frontal cortex, and is in line with a better precondition for mental work by lowering the level of basic delta activity. The lower the level the more delta can be produced in the presence of mental loads (Schober et al 1995).

Theta activity increased in response to the attenuation of the noradrenaline (norepinephrine) system arising from the locus coeruleus, due to the activity of the presynaptic adrenergic alpha2 receptor (Dimpfel & Schober 2001). A decrease in theta activity must therefore be interpreted as an activation of central noradrenaline transmission, signalling arousal, consistent with the ability to develop a state of higher concentration. Evidence for this interpretation also comes from results reported by Bjorklund et al (1998).

Electrical activity within the alpha1 frequency band obviously is under control of the serotonergic system, as reported earlier using the same rat model (Dimpfel et al 1989). In man alpha1 power has been seen to change with attention whereby increases seem to code for lower attention and decreases of power for higher attentive states.

Furthermore, alpha2 frequencies reflect changes of the dopaminergic system. This has been illustrated by studies with L-dopa or dopaminergic agonists (Dimpfel et al 1987; Dimpfel 2006). Effects of L-theanine on the release of dopamine in the striatum have been reported in the literature (Yokogoshi et al 1998). Decreases of alpha2 activity, in general, are consistent with an increased state of active working memory in man (Klimesch et al 2005). The strong decreases within this frequency in the frontal cortex and in the hippocampus could signal the induction of such a psychophysiological state in the presence of this green tea extract.

Beta1 activity might be under the control of the glutamatergic system. Decreases have been observed in the presence of stimulating drugs (Dimpfel 2003).

Fastest beta2 activity could reflect GABAergic transmission, since all sedative compounds show such increases of beta2 power in rat and man. Beta2 changes have not been observed in this study.

Since no single neurotransmitter is solely responsible for behaviour, the relationship or balance between these frequencies seems to be important for the psychophysiological state of the brain. The observed differences with respect to the electrical changes observed under different psycho-physiological situations have led us to the hypothesis that the balance of neurotransmitter action is reflected in changes of frequency content of the field potentials, i.e. the "electrical fingerprint" or electropharmacogram probably represents the activity of ion channels as governed by local transmitter action with respect to a whole local population of neurons. According to the decreases of spectral power as observed in the presence of the total extract or its single components a stimulating effect must be assumed. This is corroborated by the motion data showing an increase during the first hour in the presence of theogallin and L-theanine. However, data were not statistically significant. The late decrease of motion in the presence of L-theanine could be explained by the fact that resorption of L-theanine was slow and peak plasma levels were reached at about this time (Unno et al 1999).

In summary, the present L-theanine-enriched green tea extract had several physiologically active components, which all led to decreases of electrical power. The decrease of delta and alpha2 spectral power especially pointed to increases of dopaminergic activity, suggesting stimulating effects. The electropharmacogram of the whole extract resembled very much that of amphetamine, but only theogallin and its presumable metabolite quinic acid produced a small statistically insignificant increase of motion. Late effects of theanine with respect to motion were more recognized as an attenuation (Table 3), but data on motion showed a great variation and were not statistically significant for the extract or its constituents in comparison with saline. Therefore no relation could be seen to spectral frequency changes.

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