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Clinical Neurophysiology 145 (2023) 81–88

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Co-ultramicronized palmitoylethanolamide/luteolin normalizes $GABA_B$-ergic activity and cortical plasticity in long COVID-19 syndrome

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HIGHLIGHTS

- Long Covid patients with fatigue and cognitive problems show impairment of cortical $GABA_B$ activity and reduced plasticity in primary motor cortex.
- Co-ultramicronized palmitoylethanolamide with luteolin (PEA-LUT) 700 + 70 mg bid for 8 weeks restores $GABA_B$ neurotransmission and cortical plasticity.
- PEA-LUT is a candidate for the treatment of long Covid patients.

ARTICLE INFO

Article history:
Accepted 31 October 2022
Available online

Keywords:
Palmitoylethanolamide
Long Covid
Transcranial magnetic stimulation
Long-interval intracortical inhibition
LTP-like cortical plasticity

ABSTRACT

Objective: Transcranial magnetic stimulation (TMS) studies showed that patients with cognitive dysfunction and fatigue after COVID-19 exhibit impaired cortical $GABA_B$-ergic activity, as revealed by reduced long-interval intracortical inhibition (LICI).

Aim of this study was to test the effects of co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT), an endocannabinoid-like mediator able to enhance GABA-ergic transmission and to reduce neuroinflammation, on LICI.

Methods: Thirty-nine patients (26 females, mean age 49.9 ± 11.4 years, mean time from infection 296.7 ± 112.3 days) suffering from persistent cognitive difficulties and fatigue after mild COVID-19 were randomly assigned to receive either PEA-LUT 700 mg + 70 mg or PLACEBO, administered orally bid for eight weeks. The day before (PRE) and at the end of the treatment (POST), they underwent TMS protocols to assess LICI. We further evaluate short-latency afferent inhibition (SAI) and long-term potentiation (LTP)-like cortical plasticity.

Results: Patients treated with PEA-LUT but not with PLACEBO showed a significant increase of LICI and LTP-like cortical plasticity. SAI remained unaffected.

Conclusions: Eight weeks of treatment with PEA-LUT restore $GABA_B$ activity and cortical plasticity in long Covid patients.

Abbreviations: TMS, transcranial magnetic stimulation; GABA, gamma-aminobutyric acid; PEA, palmitoylethanolamide; LUT, luteolin; PEA-LUT, palmitoylethanolamide co-ultramicronized with luteolin; LICI, long-interval intracortical inhibition; bid, *bis in die*; SAI, short-latency afferent inhibition; LTP, long-term potentiation; 2-AG, 2-arachidonoylglycerol; PCR, polymerase chain reaction; FSS, Fatigue Severity Scale; PCDS, Perceived Cognitive Difficulties Scale; MoCA, Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; MEP, motor evoked potential; FDI, first dorsal interosseous; RMT, resting motor threshold; iTBS, intermittent theta burst stimulation.

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https://doi.org/10.1016/j.clinph.2022.10.017

Significance: This study confirms altered physiology of the motor cortex in long COVID-19 syndrome and indicates PEA-LUT as a candidate for the treatment of this post-viral condition.

1. Introduction

Approximately 30% of individuals affected by COVID-19 including asymptomatic cases (Tenforde et al., 2020), and approximately 80% of hospitalized patients (Huang et al., 2021) may experience post-COVID sequelae including fatigue and cognitive impairment, along with other ongoing neuropsychiatric (e.g. depression) (Renaud-Charest et al., 2021) and physical (e.g. dyspnea) manifestations.

Symptoms may persist following the acute illness or may first appear after recovery from the initial disease and may fluctuate or relapse over time (Soriano et al., 2022).

Persons struggling with the effects of the so-called "post-acute COVID-19 syndrome" or "long Covid" may have noticeable troubles with attention, memory, and executive function, with a high impact on quality of life (Nalbandian et al., 2021). Cognitive symptoms are likely due to the dysfunction of frontostriatal and/or frontoparietal brain networks. An MRI study showed a reduction in grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus in a large sample of patients presenting cognitive decline after mild COVID-19 (Douaud et al., 2022). 18FDG-PET/CT studies revealed hypometabolism of frontal regions, including the olfactory gyrus (Guedj et al., 2021; Sollini et al., 2021). The neurophysiological alterations at cortical level are still partially obscure.

We have recently demonstrated by using paired-pulse transcranial magnetic stimulation (TMS) protocols in patients who developed fatigue and dysexecutive syndrome after severe COVID-19 a remarkable impairment of intracortical $GABA_B$ergic activity, as shown by altered long-interval intracortical inhibition (LICI) (Ortelli et al., 2022; Versace et al., 2021). Subsequently, we were able to demonstrate similar alterations in patients with persistent fatigue and cognitive complaints after mild symptomatic COVID-19 (Ortelli et al., 2022).

Hypothesized mechanisms for such neurological alterations include direct viral damage, microvascular injury, persistent immune activation, and especially misguided host immunologic responses(Apple et al., 2022) leading to persistent neuroinflammation. Several animal and clinical studies have previously highlighted the therapeutic potential of ultramicronized palmitoylethanolamide (PEA) in various neurological diseases (Andresen et al., 2016; Beggiato et al., 2019; Caltagirone et al., 2016; Cordaro et al., 2020; Lunardelli et al., 2019; Onesti et al., 2019; Palma et al., 2016; Petrosino and Di Marzo, 2017). Interestingly, ultramicronized PEA reduced inflammatory, oxidative and coagulative alterations in the acute stage of COVID-19 (Albanese et al., 2022) and improved COVID-19-related olfactory dysfunction (Di Stadio et al., 2022). Moreover, a recently recognized PEA function is the enhancement of GABA neurotransmission through modulation of the release of the endocannabinoid 2-arachidonoylglycerol (2-AG) (Musella et al., 2017).

Hence, we conducted a double-blind, placebo-controlled, randomized clinical trial (RCT) to investigate the effects of an 8-week oral therapy cycle with palmitoylethanolamide (PEA) co-ultramicronized with the flavonoid luteolin (PEA-LUT) in patients with cognitive complaints and fatigue after mild COVID-19. We hypothesized that PEA-LUT could restore intracortical $GABA_B$-ergic neurotransmission measured by LICI.

2. Methods

2.1. Participants

The study was conducted at the 'long Covid' outpatient clinic of the Department of Neurorehabilitation (Hospital of Vipiteno, SABES-ASDAA) between September 2021 and March 2022.

Inclusion criteria were (a) previous diagnosis of SARS-CoV-2 infection confirmed through detection of virus RNA by polymerase chain reaction (PCR) testing of a nasopharyngeal swab; (b) subsequent recovery from infection as defined by two consecutive negative PCR tests separated by at least one day; (c) mild form of COVID-19 (symptoms might include fever, cough, sore throat, malaise, myalgia, anorexia, nausea, diarrhea, anosmia and ageusia) without necessitating hospital admission; (d) complaints of sense of fatigue and/or cognitive difficulties persisting after SARS-CoV-2 infection documented through following self-administered questionnaires: Fatigue Severity Scale (FSS) and Perceived Cognitive Difficulties Scale (PCDS). FSS is a self-administered 9-item questionnaire that investigates the severity of fatigue in different situations during the previous week and ranks perceived severity on a 7-point Likert scale (1 = "strongly disagree"; 7 = "strongly agree"); FSS sum score ranges from 7 to 63, the cut-off for pathology and for inclusion in the study was FSS > 36) (Krupp et al., 1989). The PDCS scale assesses perceived cognitive difficulties (referring to one or more of the following: forgetfulness, cloudiness, difficulty in focusing, thinking and communicating) on a 4-point Likert-scale: 0 = "I have no cognitive difficulties"; 1 = "I have slightly more cognitive difficulties than before COVID"; 2 = "I have moderate cognitive difficulties most of the time; 3 = "I have persistent cognitive difficulties" (Ortelli et al., 2022). PDCS score $\geq$ 1 were considered for inclusion in the study.

No restrictions were considered regarding the interval between disease onset and study participation.

Exclusion criteria were (a) prior or concurrent diagnosis of neurological, psychiatric, endocrine, metabolic or cardiopulmonary conditions; (b) clinical and/or radiological evidence of COVID-19 related pneumonia during the active phase of the disease; (c) anaemia; (d) pharmacological treatment with corticosteroids, antihistamines, antihypertensives, diuretics, antidepressants, anxiolytic or hypnotic drugs during the time of study.

Thirty-nine patients (mean age 49.9 ± 11.4 years, 26 females, mean education 13.4 ± 2.9 years, mean time from onset 296.7 ± 1 12.3 days) fulfilling the inclusion criteria were enrolled. Thirty-four patients were studied (five patients withdrew from the study after pre-intervention assessment). Their demographic and clinic characteristics are shown in Table 1. All patients were right-handed.

2.2. Study design

This randomized controlled trial (RCT) investigated the neurophysiological and cognitive impact of PEA-LUT administration in patients complaining of cognitive difficulties and fatigue after mild COVID-19 (henceforth "long Covid patients").

The study was registered with clinicaltrials.gov (NCT05311852) on April 5, 2022 with "Actual Study Start Date" August 16, 2021 and "Actual Study Completion Date" March 15, 2022.

Patients were assigned to one of two study groups (n = 17 each), receiving either PEA-LUT (Glialia®, 700 mg + 70 mg, sublingual microgranule formulation, Epitech Group SpA, Saccolongo, Italy) or PLACEBO (sublingual inert microgranules), administered orally bid for eight weeks. Glialia® is licensed in Italy as an oral food product for special medical purposes, with anti-inflammatory and neuroprotective properties.

Group allocation was centralized and occurred in a pseudo-randomized manner taking into account a balance of age, gender, education, and duration of illness (Table 1).

All participants underwent neurophysiological and neuropsychological assessment the day before beginning treatment (pre-treatment evaluation, PRE) and at the end of eight weeks PEA-LUT or PLACEBO administration (post-treatment evaluation, POST).

The study was approved by the local ethics committee (Comitato Etico dell'Azienda Sanitaria dell'Alto Adige, n. 99-2021) and was in accordance with the code of ethics of the World Medical Association . Written informed consent was obtained from all participants for the use of their clinical data for scientific purposes.

Primary outcome measure for PEA-LUT effects was the intracortical $GABA_B$-ergic neurotransmission indexed with LICI. Secondary neurophysiological outcome measures were short-latency afferent inhibition (SAI) and long-term potentiation (LTP)-like cortical plasticity. As further exploratory outcomes, we also searched for modification in cognitive performance.

2.3. Neurophysiological and cognitive assessment

We recorded motor evoked potentials (MEPs) from first dorsal interosseus (FDI) muscle of the dominant side. TMS of the dominant primary motor cortex (M1) was performed with a high-power Magstim 200 (Magstim Co., Whitland, UK), through a 7 cm figure-of-eight coil, held over the optimum scalp position to elicit maximal MEPs for a given intensity in contralateral FDI, with a posterior-to-anterior current flow (Rossini et al., 1994; Rossini et al., 2015). Stimulation intensities were expressed as a percentage of maximum stimulator output (% MSO). Surface electromyography signals were band-pass filtered (3–3000 Hz) and amplified with a Digitimer D440-4 amplifier (Digitimer Ltd., Welwyn Garden City, UK). Single sweeps were digitized (sampling rate 10 kHz) and recorded on a computer for post-hoc analysis using a CED 1401 A/D converter and Signal 6 software (Cambridge Electronic Design, Cambridge, UK). Resting motor threshold (RMT) was defined as previously described (Rossini et al., 2015).

Paired-pulse TMS was used to investigate LICI at interstimulus interval (ISI) 100 ms with a stimulation intensity of 130% RMT for both conditioning and test stimulus (Valls-Solé et al., 1992). The chosen ISI was the most effective in highlighting altered LICI in previous studies on long Covid patients (Ortelli et al., 2022; Versace et al., 2021). LICI is considered to be a phenomenon dependent on slow inhibitory postsynaptic potentials mediated through $GABA_B$-receptors (Ziemann et al., 2015).

SAI was used to evaluate M1 inhibition induced by sensory afferents. SAI is a marker of inhibitory sensorimotor integration that depends mainly on the excitatory effect of cholinergic thalamocortical projections onto the inhibitory GABAergic cortical network (Tokimura et al., 2000). The conditioning stimulus was delivered to the ulnar nerve at the wrist (at an intensity just above the motor threshold for evoking a visible twitch in FDI) and preceded the TMS by an ISI corresponding to the latency of the N20 component of the ulnar nerve somatosensory evoked potential (Di Lazzaro et al., 2007). The intensity of the TMS test pulse over M1 was adjusted to elicit stable MEPs of approximately 1 mV peak-to-peak amplitude in the relaxed FDI.

For both LICI and SAI, twenty stimuli were delivered both to elicit test and conditioned MEPs in a pseudo-randomized sequence.

Table 1
Comparison of demographic data between long COVID-19 patients in the co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT) group and in the PLACEBO group. Results are reported as mean (standard deviation). *P*-values are from the Mann-Whitney *U*-test or Chi-square test as appropriate. FSS, Fatigue Severity Scale; PCDS, Perceived Cognitive Difficult Scale.

	PEA-LUT	PLACEBO	*P*-values
Age *(years)*	53.5 (10.4)	48.1 (10.7)	0.245
Sex (female/male, *number*)	11/6	11/6	1.000
Education *(years)*	13.7 (2.5)	13.5 (2.9)	0.683
Time from onset *(days)*	291.4 (137.4)	290.2 (97.7)	0.658
FSS	47.8 (10.9)	48.2 (9.2)	0.119
PCDS	1.8 (0.7)	1.6 (1.1)	0.906

For all protocols, the mean amplitude of the conditioned responses was expressed as a percentage of the corresponding mean unconditioned response.

Finally, we used a TMS protocol assessing LTP-like cortical plasticity, consisting in potentiation of MEPs after a session of excitatory repetitive TMS (rTMS) given as intermittent theta burst stimulation (iTBS). This iTBS protocol consisted of 3 TMS pulses at 50 Hz, repeated every 200 ms (5 Hz) for 2 s. Such a 2-s train of iTBS was repeated 20 times, every 10 s, for a total of 190 s (600 pulses) (Huang et al., 2005). The intensity of iTBS was set at 70% of RMT.

To measure LTP, we considered the mean peak-to peak amplitude of 20 MEPs in relaxed FDI collected with single-pulse TMS at 120% RMT stimulation intensity, ISI of 5 s, before (T_0) and 1, 10, and 20 min after iTBS (LTP T_1, T_{10}, T_{20}).

Global cognition was assessed with the Italian version of Montreal Cognitive Assessment (MoCA) (Santangelo et al., 2015); MoCA total score ranges from 0 (worst performance) to 30 (best performance), scores below 15.5 points are indicative of cognitive decline.

Executive functions were evaluated with the Italian version of the Frontal Assessment Battery (FAB) (Appollonio et al., 2005). FAB consists of six subtests exploring specific cognitive or behavioral domains related to the frontal lobes; each subtest is scored from 0 (worst performance) to 3 (best performance), for a maximum score of 18; FAB scores lower than 13.48 are considered abnormal.

2.4. Statistics

Central tendency and dispersion of continuous variables are reported as mean and standard deviation (SD) for demographical and neuropsychological data and as mean and standard error (SE) for neurophysiological outcomes. Descriptive statistics for categorical variables are reported as number and percentage. Between-group comparisons were carried out by the Mann-Whitney U-test for continuous variables and by the Chi-square test for dichotomous variables.

The effect of treatment over time for percent change in LICI, percent change in SAI, change in MEP amplitude in the LTP-like cortical plasticity test, and neuropsychological scores (MoCA, FAB) was investigated by a two-factor analysis of variance (ANOVA), the first factor being treatment (between-group factor, two groups: PEA-LUT and PLACEBO) and the second factor being time (within-group factor, two measurements: PRE and POST), with repeated measurements in the time factor (repeated measures ANOVA). Mauchly's test was used to assess the sphericity assumption, and the Greenhouse-Geisser correction was applied if appropriate. A significant result from repeated measures ANOVA was followed up by post-hoc analysis for pairwise comparisons (Dunn-Sidak).

All tests were two-tailed. A p value < 0.05 was considered statistically significant. All statistical analyses were carried out using the

SAS/STAT statistical package, release 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 34 post COVID-19 patients completed the evaluation sessions. Demographic and clinical data are depicted in Table 1. An equal proportion of the female population (64.7%) was present in both groups. Patients did not differ significantly with respect to age, education, or time since onset of disease, FSS and PCDS. PEA-LUT and PLACEBO treatment was well-tolerated by all patients, and no side effects were reported.

3.1. Neurophysiological and cognitive assessment

All neurophysiological findings with repeated measures ANOVA results are reported in Table 2 and illustrated in Figs. 1 and 2.

In LICI protocol performed at PRE, mean test MEP amplitude for the PEA-LUT group and for the PLACEBO group were 0.93 ± 0.42 mV and 0.86 ± 0.43 mV, respectively.

In LICI protocol performed at PRE, mean test MEP amplitude for the PEA-LUT group and for the PLACEBO group were 0.90 ± 0.43 and 0.82 ± 0.43, respectively.

A significant interaction (treatment × time) was observed in the percent change of conditioned MEP amplitude in the LICI test. This finding indicates a different trend of this variable in PEA-LUT patients as compared to patients in the PLACEBO group. Indeed, post-hoc analysis revealed a significant increase in the amount of inhibition of the conditioned MEP from PRE to POST in the PEA-LUT group ($P = 0.009$) but not in the PLACEBO group ($P = 0.72$).

In SAI protocol performed at PRE, mean test MEP amplitude for the PEA-LUT group and for the PLACEBO group were 0.88 ± 0.36 mV and 0.84 ± 0.35 mV, respectively.

In SAI protocol performed at POST, mean test MEP amplitude for the PEA-LUT group and for the PLACEBO group were 1.01 ± 0.32 mV and 0.81 ± 0.40 mV, respectively.

No significant treatment or time effect and no interaction were found, indicating no differences in this variable in PEA-LUT and PLACEBO patients.

Repeated measures ANOVA for MEP amplitude modulation in the LTP-like cortical plasticity test revealed a significant interaction (treatment × time) 1 and 10 minutes following iTBS. Post-hoc testing revealed a significant increase of the MEP amplitude from PRE to POST in the PEA-LUT group but not in the PLACEBO group ($P = 0.0009$ and $P = 0.01$, for 1 and 10 minutes, respectively, in the PEA-LUT group, $P = 0.38$ and $P = 0.56$ for 1 and 10 minutes, respectively, in the PLACEBO group. No significant treatment or time effect and no interaction was observed 20 minutes following iTBS.

RMT was 52.5 (6.1) and 52.5 (10.6) %MSO in PEA-LUT and PLACEBO groups, respectively, at time PRE, which was not significantly different from POST: 52.4 (8.1) and 51.4 (8.5) %MSO in PEA-LUT and PLACEBO groups, respectively.

Results of cognitive tests are shown in Table 2. No significant interaction (treatment × time) was found in MoCA and FAB cognitive screening tests.

4. Discussion

In the present RCT oral PEA-LUT 700 + 70 mg administered bid for eight weeks increased the $GABA_B$ergic activity of M1 measured with the LICI protocol in patients complaining of long-term fatigue and cognitive difficulties after mild COVID-19 (long Covid patients). In parallel, we also observed an improvement of LTP-like cortical plasticity.

The pathogenesis of long Covid has not yet been elucidated; potential contributors include persistent consequences of SARS-CoV-2 interactions with host microbiome/virome, clotting/coagulation issues, dysfunctional brainstem/vagus nerve signaling, neuro-inflammation, ongoing activity of primed immune cells, autoimmunity, dysregulation of the renin–angiotensin–aldosterone system, and endothelial cell damage (Nalbandian et al., 2021; Proal and VanElzakker, 2021).

Animal and organoid model studies have shown that SARS-CoV-2 is able to reach and infect cells of the central nervous system (CNS) and to produce neuro-inflammation (Song et al., 2020; Song et al., 2021).

In severe COVID-19 patients, encephalopathy is associated with systemic hyper-inflammation mainly provoked by an aberrantly excessive innate immune response (Gustine and Jones, 2021). Entry of pro-inflammatory cytokines (mostly IL-1β, IL-6, TNFα, and IL-17) into the CNS via disrupted blood–brain barrier may alter glial cell function, leading to microglial activation and proliferation (Najjar et al., 2020). Similar pathophysiological mechanisms could also underlie long-term neurological symptoms after mild COVID-19 (Phetsouphanh et al., 2022).

PEA is a saturated N-acylethanolamide belonging to the family of endocannabinoids, naturally produced in the body, and largely found in several food sources which can exert anti-inflammatory and neuroprotective effects (Petrosino and Di Marzo, 2017).

In recent years, several experimental pre-clinical and clinical studies have indicated that ultramicronized PEA (a formulation

Table 2
Results from repeated measures ANOVA for neurophysiological (upper part) and neuropsychological (lower part) data. Descriptive statistics are reported as mean (SE) for neurophysiological outcomes and as mean (SD) for neuropsychological outcomes.

TEST	PEA-LUT		PLACEBO		ANOVA interactiontime × treatment	
	PRE	POST	PRE	POST	*F*-value	*P*-value
Neurophysiological results						
Intracortical circuits						
LICI (% of test amplitude)	66.6 (6.1)	32.4 (5.8)	66.8 (9.2)	71.2 (15.8)	4.9216	**0.034**
SAI (% of test amplitude)	70.9 (7.8)	65.8 (6.0)	66.1 (5.5)	70.7 (6.2)	0.6990	0.41
LTP-like synaptic plasticity						
MEP amplitude (mV) - T_0	0.85 (0.08)	0.99 (0.10)	0.91 (0.12)	0.79 (0.11)	2.9595	0.10
MEP amplitude (mV) - T_1	0.89 (0.08)	1.30 (0.10)	0.94 (0.12)	0.84 (0.13)	10.2947	**0.003**
MEP amplitude (mV) - T_{10}	0.79 (0.09)	1.11 (0.06)	0.87 (0.14)	0.80 (0.14)	5.5227	**0.025**
MEP amplitude (mV) - T_{20}	0.79 (0.09)	0.87 (0.06)	0.93 (0.17)	0.78 (0.16)	1.7757	0.19
Neuropsychological evaluation - Behavioral and cognitive screening						
MoCA	24.2 (3.2)	25.9 (2.9)	25.1 (2.8)	26.1 (2.6)	0.5222	0.48
FAB	15.9 (1.5)	16.5 (1.3)	16.5 (1.3)	17.4 (0.9)	0.978	0.330

PEA-LUT, co-ultramicronized palmitoylethanolamide/luteolin; LICI, long-interval intracortical inhibition; SAI, short-latency afferent inhibition; LTP, long-term potentiation; MEP, motor evoked potential; MoCA, Montreal Cognitive Assessment score; FAB, Frontal Assessment Battery.

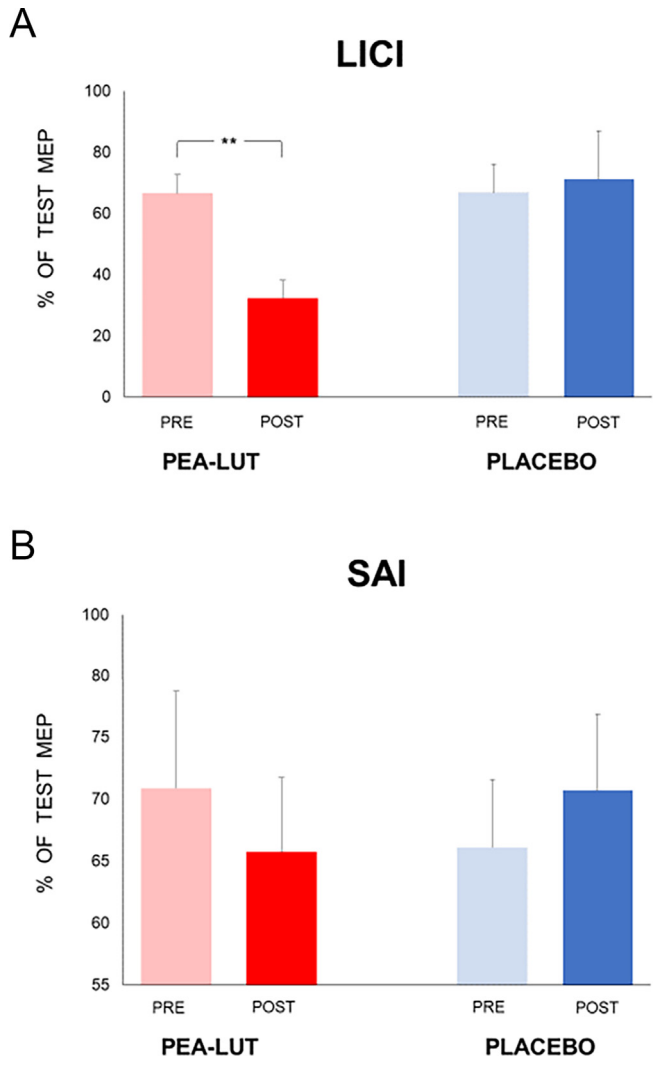

Fig. 1. Results of transcranial magnetic stimulation (TMS)-protocols for long-interval intracortical inhibition (LICI) at interstimulus interval (ISI) 100 ms (A) and short-latency afferent inhibition (SAI) at an ISI corresponding to the latency of the N20 component of the ulnar nerve somatosensory evoked potentials (B) in co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT) and PLACEBO patient groups. The columns represent the amplitude of conditioned motor evoked potentials (MEPs) expressed as percentage of the corresponding mean unconditioned response in PRE and POST conditions. Whiskers represent standard error. ** $P = 0.009$ in post-hoc testing.

that maximizes PEA bioavailability and penetrance through the blood–brain barrier) is an effective therapeutic agent in different pathologies characterized by neurodegeneration and neuroinflammation such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, spinal cord injury, and traumatic brain injury (Assogna et al., 2020; Assogna et al., 2022; Beggiato et al., 2019; Cordaro et al., 2020, Petrosino and Di Marzo, 2017). It has been proposed that PEA-LUT prevents nervous tissue damage and counteracts the hypofunction of GABAergic interneurons by reducing the activation of mast cells, astrocytes, and microglia, and by limiting the release of pro-inflammatory mediators (Cordaro et al., 2020).

Moreover, PEA is able to enhance GABA-ergic transmission down-regulating the synthesis of the endocannabinoid 2-AG, which acts retrogradely onto presynaptic CB1 cannabinoid receptors and suppresses GABA release. PEA can also control GABA transmission enhancing indirectly the levels of other endocannabinoids, through the so-called entourage effect (Kano, 2014; Musella et al., 2017).

Based on this evidence, we decided to investigate the impact of the oral administration of PEA-LUT on cortical $GABA_B$-ergic activity of long Covid patients with fatigue and cognitive difficulties. In fact, we have already demonstrated an impairment of $GABA_B$-ergic neurotransmission within M1, indexed by LICI, and to a lesser extent, of central cholinergic circuits, assessed by SAI, after both severe (Versace et al., 2021) and mild COVID-19 (Ortelli et al., 2022).

LICI is a well-known marker of $GABA_B$ mediated intracortical inhibition within M1 (Ziemann et al., 2015). As demonstrated in studies of LICI, $GABA_B$ mediated inhibition is altered in various neuropsychiatric conditions such as psychotic mood disorders, epilepsy, Parkinson's disease, traumatic brain injury, and dementia (Fatih et al., 2021). GABAergic interneurons, especially those expressing the Ca^{2+}-binding protein parvalbumin, inhibit M1 pyramidal cells through a negative feedback system (Sohal et al., 2009) and play a fundamental role in almost all neuronal coding and processing in the CNS.

Different cognitive abilities, mainly executive functions, are sensitive to cerebral GABA concentrations in the frontal cortex (Porges et al., 2017; Sumner et al., 2010). In particular, reduced LICI is now a recognized biomarker of fronto-temporal dementia (FTD) (Benussi et al., 2020) where it correlates with executive function deficit.

Interestingly, a 4-week treatment with PEA-LUT induced an improvement in frontal cognitive functions and a restoration of LICI in FTD patients (Assogna et al., 2020). Long Covid shares with FTD the impairment of executive functions (although to a different extent) and a comparable reduction of LICI (Benussi et al., 2020; Ortelli et al., 2022).

Moreover, degeneration of intracortical inhibitory GABAergic circuits within M1 has been reported in various affections of the central nervous system inducing fatigue (Liepert et al., 2005; Ridding et al., 1995; Vucic et al., 2011). In light of these studies, a downregulation of GABA activity and the consequent enhancement of cortical excitability could be seen as a compensatory mechanism for overcoming premature motor fatigue. On the other hand, one cannot exclude the possibility that cortical disinhibition is the cause of fatigue itself, as a system with upregulated excitability may have a lower range to further increase excitability.

SAI reflects M1 inhibition induced by sensory afferents and depends on the excitatory effect of cholinergic thalamocortical projections on inhibitory GABAergic cortical networks (Tokimura et al., 2000). Consolidated evidence points to a disrupted SAI mechanism in both Alzheimer's and Lewy-body disease patients, where SAI correlate with memory function (Di Lazzaro et al., 2002; Di Lorenzo et al., 2013; Nardone et al., 2006).

Important indications on the relevance of LICI and SAI paradigms to investigate neurophysiological processes in the human cortex as well as their relationship to pathology come from TMS-electroencephalography (EEG) measurements. $GABA_B$-mediated inhibition of cortical activity in M1 and dorsolateral prefrontal cortex (DLPFC) can be obtained with LICI protocols (Daskalakis et al., 2008; Farzan et al., 2010; Premoli et al., 2014). Prefrontal LICI deficits are specific to patients with schizophrenia and other neuropsychiatric disorders (Tremblay et al., 2019). The attenuation of cortical excitability induced by SAI protocols identifies cholinergic changes in M1 and DLPFC and correlates with executive functions (Bikmullina et al., 2009; Noda et al., 2017).

We tested LICI at the ISI of 100 ms, which usually yields maximum MEP inhibition (Valls-Solé et al., 1992) and which was effective in highlighting altered LICI in long Covid patients (Ortelli et al., 2022; Versace et al., 2021). We found markedly reduced LICI in a similar range to our previous studies, in which we compared long Covid patients to a control population matched for age, sex and

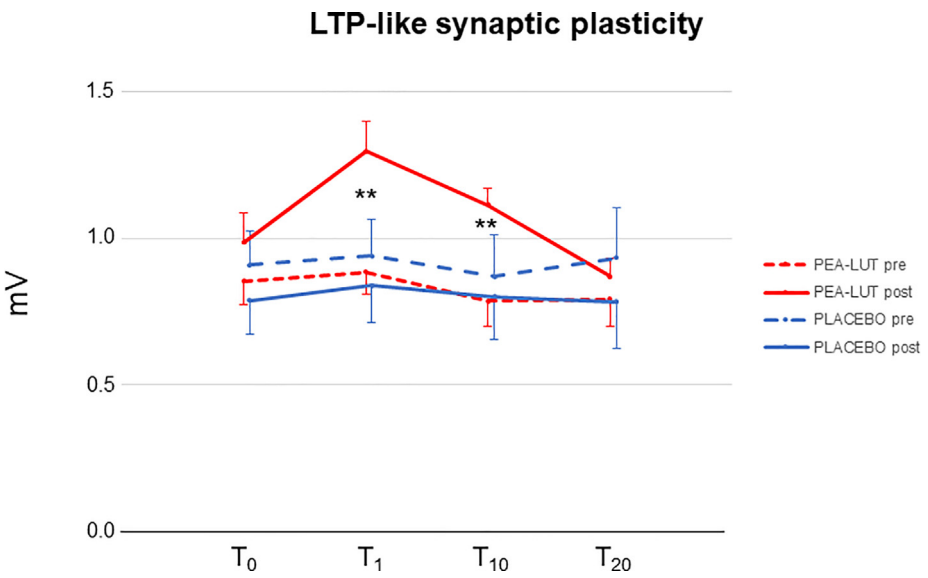

Fig. 2. The graph represents the mean amplitude of motor evoked potentials (MEPs) at baseline (T0) and after 1, 10 and 20 min (T1, T10, T20) excitatory repetitive transcranial magnetic stimulation given as intermittent theta burst stimulation (iTBS) to the primary motor cortex for 190 s (600 pulses) in co-ultramicronized palmitoylethanolamide/luteolin (PEA-LUT) (red) and PLACEBO (blue) patient groups at PRE (dashed line) and POST (solid line). A significant increase of MEP amplitude was evident 1 and 10 minutes after iTBS in the PEA-LUT group POST-treatment. ** $P = 0.0009$ and $P = 0.01$ in PEA-LUT group for T1 and T10 in post-hoc testing, respectively.

education (Ortelli et al., 2022; Versace et al., 2021). LICI increased significantly (i.e., percentage ratio of mean conditioned to mean test MEP amplitude decreased) after intervention in the PEA-LUT group, but not in the PLACEBO group.

We assessed SAI at the most effective ISI between cortical and peripheral stimulation, i.e., coinciding with the cortical somatosensory evoked potential component N20 following ulnar nerve stimulation at the wrist (Di Lazzaro et al., 2007), and found reduced SAI in line with our previous observations (Ortelli et al., 2022; Versace et al., 2021). Unlike LICI, SAI was not significantly improved by PEA-LUT therapy in the present study.

Furthermore, we investigated LTP-like cortical plasticity in M1 with the technique of rTMS given as iTBS, i.e., a stimulation with high-frequency bursts (5 Hz) at theta frequencies (50 Hz) which is able to induce homotopic plasticity (Huang et al., 2005). In rTMS studies indeed, cortical LTP-like plasticity is evidenced by the transient increase in MEP amplitude outlasting repetitive brain stimulation by seconds or minutes and reflecting activity-dependent changes in the effectiveness of synaptic transmission (Ziemann et al., 2008).

In the studied cohort of long Covid patients, iTBS failed to induce the expected potentiation of MEP amplitudes, thus indicating altered LTP-like cortical plasticity. The transient physiological MEP facilitation, however, was restored in the post-treatment evaluation only in the PEA-LUT group.

The pathophysiological cascade in patients with severe COVID-19 is related to over-stimulation of T cells and macrophages with a subsequent release of an enormous quantity of pro-inflammatory cytokines such as interleukins and chemokines that can result in multi-organ dysfunction (Yuki et al., 2020). Moreover, GABAergic neurons have a higher expression of ACE2 receptors (Chen et al., 2020; Mukerjee et al., 2019). If SARS-CoV-2 enters the brain it has the potential to access GABAergic neurons, leading to functional impairment until apoptosis and causing excitatory-inhibitory imbalance (Ramani et al., 2020). Cytokine release from infected neurons and other activated microglia and astrocytes may also cause a decrease in GABA (Galic et al., 2012). GABA-ergic transmission is also impaired in hypoxic conditions (Oliviero et al., 2002), as also seen in severe COVID-19 patients with pneumonia (Versace et al., 2021).

The different pathways mentioned above through which PEA-LUT is able to enhance GABA-ergic transmission in the central nervous system may explain its effect on the $GABA_B$-ergic (LICI) circuits found in the present study.

The molecular mechanism by which PEA-LUT improves LTP-like cortical plasticity is very likely related to the involvement of the cannabinoid system. PEA as an endocannabinoid anandamide congener, is known to modulate glutamatergic transmission mainly through cannabinoid CB1 receptor and the transient receptor potential vanilloid 1 and to restore LTP mechanisms (al-Ghoul et al., 1993; Basavarajappa et al., 2014; Boccella et al., 2019; Guida et al., 2015; Lutz et al., 2015; Zimmermann et al., 2019). Hippocampal PEA modulates reward and memory in mesolimbic areas through GPR55 receptors with the implication of glutamatergic projections emerging from ventral hippocampus (Kramar et al., 2017). Endocannabinoid signaling via anandamide or PEA is implicated in several neuronal functions and considered a potential therapeutic target for disorders associated with altered plasticity (Maccarrone, 2017; Zimmermann et al., 2019).

While we found that PEA-LUT had a beneficial impact on altered motor cortex physiology, we did not observe significant changes in the chosen cognitive measures.

MoCA and FAB, exploring global cognition and executive function respectively, exhibited a ceiling effect (Table 2) i.e. insufficient sensitivity for patients' cognitive disturbances, thus preventing the possibility of observing cognitive improvement after treatment.

Future RCTs on selected groups of patients with more pronounced cognitive impairment or using more sensitive cognitive / behavioural outcome measures will be better able to assess the clinical impact of this or other treatments. Furthermore, studies with a longer observation period could evaluate the duration of the treatment effect.

In conclusion, the present RCT demonstrates that PEA-LUT is able to enhance $GABA_B$-ergic neurotransmission and LTP-like cortical plasticity in long Covid patients.

The mechanisms of action with which PEA-LUT exerted these effects are not deducible only from the current results and can be hypothesized on the basis of previous evidence, possibly depending on the reduction of central neuroinflammation or on the direct modulation of GABA-ergic and glutamatergic activity.

Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

The data that support the finding of this study are available upon request from the corresponding author.

Acknowledgements

The authors thank the pharmaceutical company Epitech Group SpA, Saccolongo, Italy, for the free supply of the active and placebo product.

The authors also thank Annelies Gruber for her excellent administrative support and Ellen Quirbach for language editing.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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