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ORIGINAL PAPER

PDGF Modulates Synaptic Excitability and Short-Latency Afferent Inhibition in Multiple Sclerosis

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Abstract

Maintenance of synaptic plasticity reserve is crucial to contrast clinical deterioration in MS and PDGF plays a key role in this phenomenon. Indeed, higher cerebrospinal fluid PDGF concentration correlates with improved clinical recovery after a relapse, and the amplitude of LTP-like cortical plasticity in relapsing-remitting MS patients. However, LTP-like cortical plasticity varies depending on the individual level of inhibitory cortical circuits. Aim of this study was to explore whether PDGF-CSF concentration correlates with inhibitory cortical circuits explored by means of transcranial magnetic stimulation in patients affected by relapsing-remitting MS. We further performed electrophysiological experiments evaluating GABAergic transmission in the experimental autoimmune encephalomyelitis (EAE) hippocampus. Our results reveal that increased CSF PDGF concentration correlates with decreased short afferent inhibition in the motor cortex in MS patients and decreased GABAergic activity in EAE. These findings show that PDGF affects GABAergic activity both in MS patients and in EAE hippocampus.

Keywords GABA · Long term potentiation · PDGF · CSF · Paired pulse · Transcranial magnetic stimulation

Abbreviations

aCSF	Artificial cerebrospinal fluid
CFA	Complete Freund adjuvant
CNS	Central nervous system
EAE	Experimental autoimmune encephalomyelitis
ISI	Interstimulus interval
LTP	Long term potentiation
MS	Multiple sclerosis
PAS	Paired associative stimulation
PDGF	Platelet derived growth factor
RMT	Resting motor threshold
SICI	Short-interval intracortical inhibition
SAI	Short-latency afferent inhibition
sIPSC	Spontaneous inhibitory postsynaptic current
TMS	Transcranial magnetic stimulation

Introduction

In the early and acute phases of multiple sclerosis (MS), T cells accumulate in the central nervous system (CNS) and release various proinflammatory cytokines, which mediate tissue damage [1]. However, during the disease progression, immune cells also contribute to neuronal and oligodendroglial cell survival and tissue repair by secreting different growth factors [2, 3]. The release of growth factors that occurs in MS brain supports several functions, including the modulation of microglial activity and the stimulation of oligodendrocyte proliferation or regeneration within lesioned areas [4–10].

Platelet derived growth factor (PDGF) is one of many growth factors released by inflammatory cells. PDGF represents a key molecule for the recovery phase of MS because

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of its neuroprotective action [11]. Indeed, it promotes neuronal differentiation [7, 12], improves remyelination and oligodendrocyte density during acute demyelination and reduces apoptosis [11].

A strong upregulation of PDGF was described in peripheral lymphocytes of experimental MS, with the highest expression at the peak of the disease [13]. Notably, in animal studies, synaptic transmission and LTP are regulated by various growth factors, which are released by inflammatory cells and able to influence synaptic function and the clinical manifestations of MS [14, 15].

In our previous work, we have demonstrated that maintenance of synaptic plasticity reserve is crucial to contrast clinical deterioration in MS and PDGF plays a key role in this phenomenon [16]. Also, we found a correlation between the cerebrospinal fluid (CSF) PDGF concentration and the extent of clinical recovery after a relapse, as full recovery was more likely observed in patients with high PDGF concentration and poor recovery in subjects with low PDGF levels. We have also demonstrated a striking correlation between CSF levels of PDGF and the amplitude of LTP-like cortical plasticity in relapsing-remitting (RR-)MS patients, as well as between PDGF exposure and facilitation of LTP in mouse brain slices [16].

However, LTP is a complex phenomenon, and changes in cortical circuits activity may alter its induction [17–19]. Indeed, the amplitude of LTP-like plasticity induced by transcranial magnetic stimulation (TMS) through the paired associative stimulation (PAS) protocol, varies depending on the individual level of inhibitory cortical circuits [15]. TMS studies revealed that weaker PAS-induced LTP correlated with stronger GABAergic activity in the primary motor cortex as measured by short-interval intracortical inhibition (SICI) [20] and with stronger inhibitory afferent projections over the primary motor cortex as measured by short-latency afferent inhibition (SAI) [21] in healthy individuals. These findings raised the hypothesis that PDGF’s influence over PAS induced LTP may be mediated by SICI or SAI cortical circuits. Aim of this study was thus to explore whether PDGF-CSF concentration correlates with SICI and/or SAI activity in patients affected by RR-MS.

We also performed electrophysiological experiments evaluating GABAergic transmission in the experimental autoimmune encephalomyelitis (EAE) hippocampus.

Methods

Patients

The study was approved by the Ethics Committee of the University Hospital Tor Vergata (Rome, Italy). Patients gave their written informed consent before study enrollment.

To explore the correlation between PDGF and cortical excitability in RR-MS, we used the CSF collected from 27 patients, who were admitted at the neurology clinic of the University Hospital Tor Vergata of Rome between 2009 and 2015 and underwent CSF withdrawal for diagnostic purpose with a clinical suspect of RR-MS which was later confirmed. The diagnosis of MS was established by clinical, laboratory and MRI parameters, and matched published criteria [22]. Immediately after withdrawal the CSF was centrifuged and stored at − 80 °C until analyzed. Corticosteroids or other MS-specific immunoactive therapies were initiated later when appropriate.

Determination of PDGF Concentration in the Cerebrospinal Fluid (CSF)

PDGF concentrations were analyzed using Bio-Plex Multiplex Cytokine Assay (Bio-Rad Laboratories), according to manufacturer instructions. PDGF concentrations were calculated according to a standard curve generated for the specific target, and expressed as pg/ml. When the concentrations were below the detection threshold they were assumed to be 0 pg/ml.

TMS Procedure

Enrolled patients underwent TMS procedure within 24 h from CSF withdrawal to measure cortical excitability. Magnetic stimulation was performed using a high-power Magstim 200 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). A figure of eight coil with external loop diameter of 9 cm was held over the motor “hot spot” (M1) of left motor cortex defined as the optimum scalp position to elicit motor responses in the contralateral first dorsal interosseous (FDI) muscle. The optimal position was marked on the scalp with a felt pen to ensure identical placement of the coil throughout the experiment. The handle of the coil was pointed backward and laterally at about 45° to the midsagittal line of the scalp throughout the experiment.

Surface muscle responses were obtained through 9 mm diameter Ag–AgCl electrodes with the active electrode placed over the motor point of the FDI muscle and the reference on the metacarpo-phalangeal joint of the index finger. Muscle responses were amplified and filtered (bandwidth 3–10,000 Hz) through a D360 amplifier (Digitimer, Welwyn Garden City, Hertfordshire, UK). Data were collected on a computer with a sampling rate of 5 kHz and stored for off-line analysis using a CED 1401 A-D converter (Cambridge Electronics Design, Cambridge, UK).

The resting motor threshold (RMT) was defined as the lowest intensity that produced MEPs of 50 µV in at least five out of 10 trials with the muscles relaxed [23].

SICI was tested through ppTMS by delivering a subthreshold conditioning stimulus (CS) preceding a suprathreshold test stimulus (TS) [24]. Stimulus intensity was set at 80% AMT for the CS and adjusted to evoke a muscle response in the relaxed FDI with a mean amplitude of about 1 mV peak-to-peak. Three conditions were presented in a random order: control (TS given alone) and two pp conditions (TS preceded by CS) at one of two different ISIs (2 and 3 ms).

Short latency afferent inhibition (SAI) was studied as in [25] by using an electrical CS applied through bipolar electrodes (cathode proximal) to the right median nerve at the wrist preceding a TMS TS delivered over M1. The intensity of the CS was set at just over motor threshold for evoking a visible twitch of the thenar muscles. The intensity of the TS magnetic stimulus was adjusted to evoke a muscle response in relaxed right FDI with amplitude of about 1 mV peak-to-peak. The CS to the peripheral nerve preceded the magnetic TS by different interstimulus intervals (ISIs). ISIs were determined as in relative to the latency of the N20 component of the somatosensory evoked potential induced by stimulation of the right median nerve. The active electrode for recording the N20 potential was attached 3 cm posterior to C3 (10–20 system) and the reference was 3 cm posterior to C4. A total of 500 responses were averaged to identify the latency of the N20 peak. ISIs from the latency of the N20 plus 2 ms to the latency of the N20 plus 8 ms were investigated in steps of 2 ms. A total of ten stimuli were delivered at each ISI for both SICI and SAI. The subject was given audiovisual feedback at high gain to assist in maintaining complete relaxation. The inter-trial interval was set at 5 s (± 10%). Measurements were made on each individual trial. The mean peak-to-peak amplitude of the conditioned MEP at each ISI was expressed as a percentage of the mean peak-to peak amplitude size of the unconditioned test pulse in that block.

Electrophysiology

All experiments followed international guidelines on the ethical use of animals from the EU Directive 2010/64/EU. Experimental autoimmune encephalomyelitis (EAE) was induced in 6–8 weeks old female C57BL/6 mice purchased from Charles-River (Italy) as previously described [26]. EAE was induced by active immunization following subcutaneous injection with 200 mg of myelin oligodendrocyte glycoprotein p35-55 (MOG35-55) emulsion. The emulsion was prepared under sterile conditions using MOG35-55 (> 85% purity, Espikem, Florence, Italy) in complete Freund's adjuvant (CFA, Difco), and Mycobacterium tuberculosis H37Ra (8 mg/ml; strain H37Ra, Difco, Lawrence, KS, USA) emulsified with phosphate buffered saline (PBS). Control emulsion was prepared deprived of MOG35-55 for the control group (CFA group). Animals were scored daily for clinical symptoms of EAE, according to the following scale: (0) no clinical signs; (1) flaccid tail; (2) hind limb weakness; (3) hind limb paresis; (4) complete bilateral hind limb paralysis; (5) death due to EAE; intermediate clinical signs were scored adding 0.5 value. Mice were killed by decapitation and brains were rapidly dissected out and parasagittal hippocampal slices (250 µm) were cut with a vibratome (VT 1200S, Leica) in cold (0 °C) artificial cerebrospinal fluid (aCSF) containing (in mM): NaCl 124; KCl 3; $MgSO_4$ 1; $CaCl_2$ 2; Na H_2PO_4 1.25; $NaHCO_3$ 26; glucose 10; saturated with 95% O_2, 5% CO_2 (pH 7.4), and left to recover for 1 h in ACSF at 30 ± 2 °C. Slices were placed in aCSF at 33.0 ± 0.5 °C for 30 min and then maintained in aCSF at room temperature.

Whole cell patch-clamp recordings for CA1 pyramidal neurons were obtained as previously described [27]. Spontaneous inhibitory postsynaptic currents (sIPSCs) recordings were made using intracellular solution containing (in mM) KCl 145, $CaCl_2$ 0.05, EGTA 0.1, Hepes 10, Na_3-GTP 0.3, Mg-GTP 4.0, pH adjusted to 7.3 with KOH. The sIPSCs were detected in continuous presence of glutamatergic AMPAR antagonist CNQX (10 µM) and NMDAR blocker MK-801 (10 µM) to pharmacologically isolate GABA-mediated currents. The spontaneous events were detected from 3 min trace records and analyzed with Clampfit (Molecular Devices, Sunnyvale, CA, USA).

Analysis

The relationship between PDGF-CSF concentration and SAI at the ISI that produced the maximal inhibition (SAI peak) was explored through Spearman correlation analysis.

Changes in amplitude or inter-event interval of the spontaneous events were compared according to their cumulative distributions, using the Kolmogorov–Smirnov (K–S) test.

The significance level was established at $p < 0.05$.

Results

A total of 27 patients, 14 females, aged between 20 and 48 years, EDSS comprised between 0 and 4, who were diagnosed with RR-MS were recruited.

Correlation Between PDGF-CSF Concentration and Short-Latency Afferent Inhibition in RR-MS Patients

To test whether PDGF may affect inhibitory circuits in the primary motor cortex, which are known to influence PAS, we measured PDGF-CSF concentration and ppTMS SICI and SAI in our patients and tested for a correlation between them. Spearman correlation analysis revealed that PDGF-CSF concentration significantly correlated with SAI-peak (rho = 0.38; $p < 0.05$) showing that higher PDGF levels were associated to decreased SAI (Fig. 1). Conversely no significant correlation emerged between PDGF-CSF concentration and SICI at both 2 and 3 ms ISIs.

PDGF Affects GABAergic Transmission in Hippocampus via PDGF-BB Receptor

To investigate the effect of PDGF on GABAergic transmission we performed experiments in CFA slices pre-incubated with PDGF (20 ng/ml for 1 h). Neurons recorded from these slices displayed reduced GABAergic transmission, manifested as sIPSCs of reduced amplitude and larger inter-event interval. This effect was proven by the leftward shift of the cumulative sIPSCs amplitude distribution ($p < 0.001$, K–S test; Fig. 2a), combined with rightward shift of the cumulative sIPSCs inter-event interval distribution ($p < 0.001$, K–S test; Fig. 2a) of the same events in slices pre-incubated with PDGF (n = 17) compared to vehicle (n = 16). Notably, the decrease in the efficacy of GABAergic transmission by PDGF was prevented by co-incubation with the PDGF-BB receptor antagonist PZ0012 (1 µM) (n = 14; Fig. 2a). In fact, in the presence of PZ0012, sIPSCs returned to higher amplitude ($p < 0.001$, K–S test) and lower inter-event interval ($p < 0.001$, K–S test; Fig. 2a).

To assess the involvement of PDGF in the reduced GABAergic transmission previously found in the EAE model [27], we pre-incubated EAE hippocampal slices with PDGF (20 ng/ml for 1 h). Neurons recorded show similar cumulative distribution of sIPSC in amplitude and inter-event interval ($p > 0.05$, K–S test; Fig. 2b) compared to vehicle (n = 15). Notably, the pharmacological blockade of PDGF-BB receptor normalized the amplitude and inter-event interval alteration in EAE slices to levels comparable to CFA levels. This was proven by the rightward shift of cumulative amplitude distribution ($p < 0.001$, K–S test; Fig. 2b) and leftward shift of cumulative inter-event interval distribution ($p < 0.001$, K–S test; Fig. 2b).

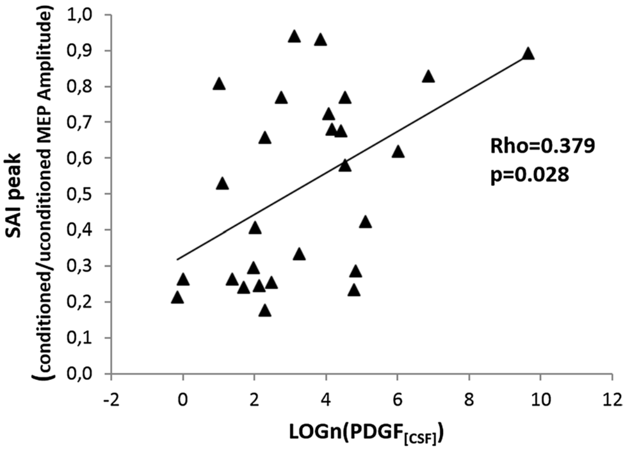

Fig. 1 Correlation between PDGF CSF levels and Short latency afferent inhibition (SAI). The figure represents the scatter plot between individual natural logarithm of PDGF-CSF levels and the SAI at the ISI that produced the maximal inhibition. It is showed how increasing levels of PDGF correlate with decreased SAI induced inhibition

To assess the role of endogenous PDGF in the reduced GABA transmission previously found in the EAE model [27], we pre-incubated hippocampal slices obtained from EAE mice in the presence of the PDGF-BB receptor antagonist PZ0012 (1 µM for 1 h) (n = 15; Fig. 2c). Notably, the pharmacological blockade of PDGF-BB receptor rescued both amplitude and inter-event interval alteration in EAE slices. This effect was demonstrated by a rightward shift of cumulative sIPSCs amplitude distribution ($p < 0.001$, K–S test; Fig. 2c), and a leftward shift of cumulative inter-event interval distribution ($p < 0.001$, K–S test; Fig. 2c). Overall these results suggest that endogenous PDGF might contribute to reduce GABAergic transmission in the EAE model.

Discussion

The present study shows a relationship between PDGF levels in the CSF and short latency afferent inhibition (SAI) in RR-MS patients. Conversely no significant correlation emerged between PDGF and SICI. SAI is a paired-pulse TMS protocol that consists in the inhibition of the MEPs by afferent sensory impulses. SAI is believed to be mediated by cholinergic projections over M1. Indeed, in normal subjects, SAI can be abolished by intravenous injection of the muscarinic antagonist scopolamine [28]. Moreover SAI is found abnormal in patients with cholinergic forms of dementia [29], and can be normalized by acetylcholinesterase inhibitors [30]. SAI is also decreased by single oral doses of benzodiazepines like lorazepam and zolpidem, but not diazepam, suggesting that some GABAA receptor subtypes are involved in SAI [31].

We have also explored the relationship between PDGF-CSF levels and SICI as SICI is a TMS protocol of cortical inhibition, which is believed to be directly related to GABAA activity. Indeed, in healthy subjects SICI is increased by single oral doses of diazepam and lorazepam [32] but not of zolpidem [31]. However, no significant correlation emerged between PDGF-CSF levels and SICI in our group of patients.

Activity of intracortical inhibitory circuits explored by SAI and SICI showed an inverse correlation with the magnitude of LTP that can be induced by PAS [20, 21]. Thus, the results of this study apparently follow our previous evidences suggesting altered cortical plasticity in MS patients [15, 16, 23]. In fact, our previous studies provided evidence

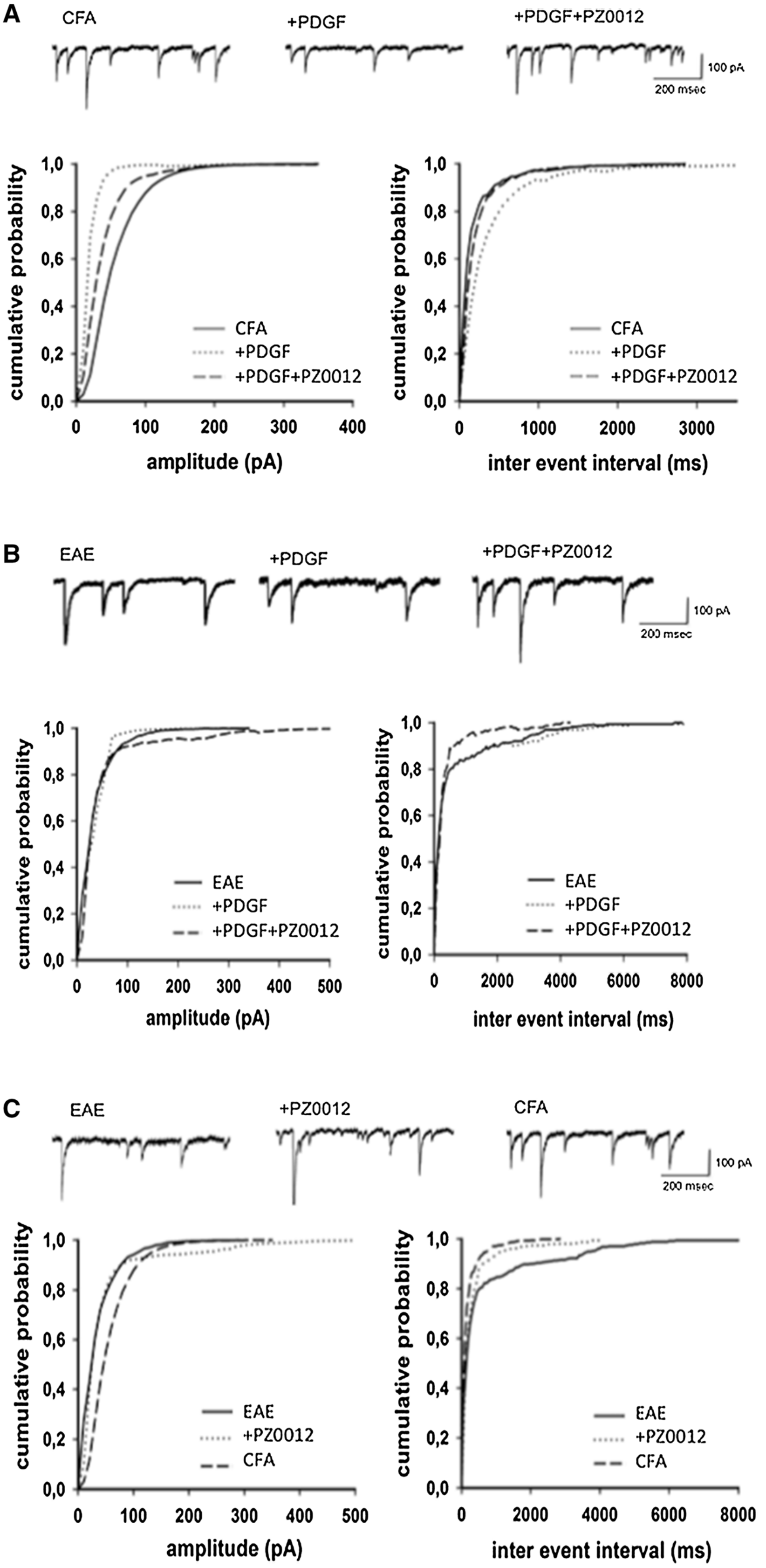

Fig. 2 Effects of PDGF on hippocampal GABAergic transmission in CFA and EAE mice. **a** Pooled cumulative distribution of sIPSCs amplitude (left; bin size 10 pA) and inter-event interval (right; bin size 50 ms) recorded in hippocampal slices from CFA controls pre-incubated with PDGF alone or PDGF plus PZ0012. On top are representative trace recordings in the different conditions. **b** Pooled cumulative distribution of sIPSCs amplitude (left; bin size 10 pA) and inter-event interval (right; bin size 50 ms) recorded from neurons of EAE or EAE pre-incubated with PDGF alone or PDGF plus PZ0012. **c** Pooled cumulative distribution of sIPSCs amplitude (left; bin size 10 pA) and inter-event interval (right; bin size 50 ms) recorded from neurons of EAE or EAE pre-incubated with PZ0012 or CFA controls

supporting the hypothesis that PDGF plays a substantial role in favoring LTP both in hippocampal slices and in MS patients, and that LTP is associated with clinically stable disease course and the possible compensation of new brain lesions formation in RR-MS [33]. Nowadays, the ability of PDGF to favor LTP is only marginally understood [14–16]. Moreover, correlation does not imply causal relationship. However, based on the notion that cortical plasticity modifications recorded in MS patients are comparable to those studied in EAE mice [27], and that a reduced GABAergic transmission is associated to enhanced LTP induction in hippocampus [27], we here further explored the relationship between PDGF and hippocampal GABAergic transmission in the EAE model. In line with the observation that inhibitory intracortical activity, as assessed through SAI, is reduced in MS patients with high levels of PDGF, we found that application of PDGF in brain slices also decreases GABAergic transmission in control animals. Of note, reduced inhibitory transmission was also observed in EAE mice, an effect which was reversed by a selective antagonist of PDGF-BB receptor. Overall, these data suggest that PDGF contributes, among other factors, to the reduction of GABAergic transmission in the EAE model.

Nevertheless, in our study, PDGF-CSF concentration failed to show a significant correlation with SICI. As GABAA agonists binding to different GABAA receptor subtypes differentially affect SICI and SAI we hypothesize that PDGF may interact only with a subset of different subtypes of GABAA receptors. During a relapse however, MS patients show decreased SICI [34] suggesting that the increased LTP responses observed in RR-MS patients may possibly be secondary to changes in excitatory or inhibitory synaptic transmission activity. In this respect, reduction of cortical inhibition has been proposed as a mechanism to augment plastic properties [35, 36]. Accordingly, LTP is potentiated by reducing GABA transmission [37, 38] which, we argue, may be mediated by an increased release of cytokines such as PDGF during MS. The ability to modulate synaptic plasticity has been also described for other growth factors such as insulin-like growth factor I (IGF-I) and brain derived neurotrophic factor (BDNF) [39, 40]. IGF-I showed antidepressant and anxiolytic effects in humans and its plasma levels are positively correlated with positive affective states and negatively correlated with depression scores [41, 42]. In experimental model of depression IGF-I produces its antidepressant effect acting through potentiation of glutamatergic synaptic transmission and facilitation of LTP [43]. Similarly, converging evidence strongly suggest that deficits in BDNF signaling underlies the pathogenesis of several brain disorders including Alzheimer's disease and depression. Indeed it is well established that BDNF is a critical mediator in antidepressant action [44]. Of note, it has been shown that BDNF levels increased significantly after MS relapse, further suggesting that also this neurotrophin might promote the recovery of acute demyelinating inflammatory lesion [45].

Cortical excitability may thus result from a complex interplay between a number of factors. Indeed, alterations of SAI have been observed in association with cognitive deficits [46–48], movement preparation [49], modifications of cholinergic [48], GABAergic [50] and dopaminergic activity [51]. This may also account for the weak, although significant, correlation that we here report between SAI and PDGF-CSF.

In the light of these evidences it is possible to speculate that PDGF may contribute to compensation of brain damage in RR-MS patients by promoting mechanisms of adaptive plasticity through the reduction of inhibitory inputs within the brain.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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