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Pharmacophysiology of TMS-evoked EEG potentials: A mini-review

Introduction

The electroencephalographic (EEG) response to transcranial magnetic stimulation (TMS) has been recognized as a direct measure of excitation, inhibition and effective connectivity of human cortex. TMS of primary motor cortex (M1) generates a series of positive and negative deflections in the scalp EEG, which result from temporal and spatial summation of excitatory and inhibitory postsynaptic potentials. These TMS-evoked potentials (TEPs) are highly reproducible across different studies and are named based on their polarity (positive (P) or negative (N)) and latencies (in milliseconds): P25, N45, P70, N100, and P180 (Fig. 1). TEPs with latencies <25 ms are not consistently reported due to contamination of the EEG by the residual TMS artifact. Early TMS-EEG studies led to the following hypotheses: The P25 may represent a local excitatory response of the stimulated M1 because its amplitude is correlated with the amplitude of motor evoked potentials (MEPs) recorded with electromyography (EMG) from a contralateral hand muscle. The N100 may represent an inhibitory response because its amplitude is correlated with the duration of the cortical silent period, a single-pulse TMS-EMG measure of gamma-aminobutyric acid type B receptor (GABAR)-mediated cortical inhibition, and is attenuated during voluntary movement preparation. Despite these initial findings, the neurophysiological underpinnings of TEPs are still only rudimentary understood. Recent pharmacological TMS-EEG studies shed more light on the mechanisms of TEPs. In these studies TEPs have been compared before and after administration of a single dose of a study drug with a specific mode of action in randomized, placebo-controlled, double-blind crossover designs in healthy subjects. This mini-review highlights these pharmaco-TMS-EEG findings to provide a more advanced picture of the physiology of TEPs.

Pharmacology of TEPs evoked by single-pulse TMS of M1

These studies used single-pulse TMS of M1 mostly at a stimulus intensity of 100% resting motor threshold (RMT), and a focal figure-of-eight coil placed tangentially on the scalp 45° away from the midline, resulting in induced current from lateral-posterior to medial-anterior. The pharmacophysiological findings from the currently available studies are summarized in Fig. 1 and Table 1 and are detailed below separately for each of the TEPs.

P25: Carbamazepine, a voltage-gated sodium channel (VGSC) blocker, suppressed the P25 amplitude at the site of stimulation [1]. This reduction was significant with and without increasing stimulus intensity to adjust for changes in RMT after carbamazepine intake. Therefore, membrane excitability regulated by VGSCs contributes to the P25. Findings are in line with an exaggerated P25 amplitude in patients with progressive myoclonus epilepsy, indicating cortical hyperexcitability, and with the direct relation of P25 amplitude with excitability of the corticospinal system (MEP amplitude).

N45: Alprazolam and diazepam (classical benzodiazepines, positive modulators of GABAARs), zolpidem (positive modulator of the α1-GABAARs) [2], and dextromethorphan, a competitive N-methyl-D-aspartate receptor (NMDAR) antagonist [3] all increased N45 amplitude over the frontal cortex of the non-stimulated hemisphere, where the N45 is most expressed. In contrast, S44819 (experimental compound, competitive selective α5-GABAAR antagonist) specifically decreased N45 amplitude [4]. These complementary findings strongly suggest that a balance of inhibitory GABAAergic and excitatory glutamatergic neurotransmission determines the N45 amplitude in the non-stimulated hemisphere.

P70: Perampanel (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) antagonist) suppressed P70 amplitude in the non-stimulated hemisphere [3], supporting the notion that this propagated activity is controlled by fast glutamatergic neurotransmission through AMPARs.

N100: Baclofen (specific GABABR agonist) increased the N100 amplitude at the site of the stimulated M1 [2]. In contrast, positive modulators of the GABAAR (alprazolam, diazepam) [2] and drugs inhibiting presynaptic excitatory neurotransmitter release (brivaracetam and levetiracetam) decreased N100 components in the non-stimulated hemisphere [1,5]. These findings support the aforementioned hypothesis that the N100 at the site of stimulation reflects long-lasting inhibition mediated by GABABRs. In contrast, N100 activity in the non-stimulated hemisphere likely represents signal propagation through interhemispheric cortico-cortical or other long-range connections, which is under the control of neurotransmission through GABAARs [6].

P180: Lamotrigine and carbamazepine (classical VGSC blockers) decreased P180 amplitude in the non-stimulated hemisphere with and without adjusting stimulus intensity to correct for the changes in RMT [1,5]. A possible contribution of multisensory (auditory and somatosensory) peripheral stimulation to remote and late TEPs cannot be entirely excluded. However, given all online and offline control conditions and previous findings that GABAergic drugs had no effect on the P180, while diazepam modulated the amplitude of auditory evoked potentials (for more details, see Ref. [1]), the possibility can be largely excluded that the reduction of P180 by VGSC blockers was due to a pharmacological modulation of residual auditory evoked potentials. Consequently, suppression of P180 under VGSC blockers likely indicates sensitivity of the late TEPs to VGSC activity.

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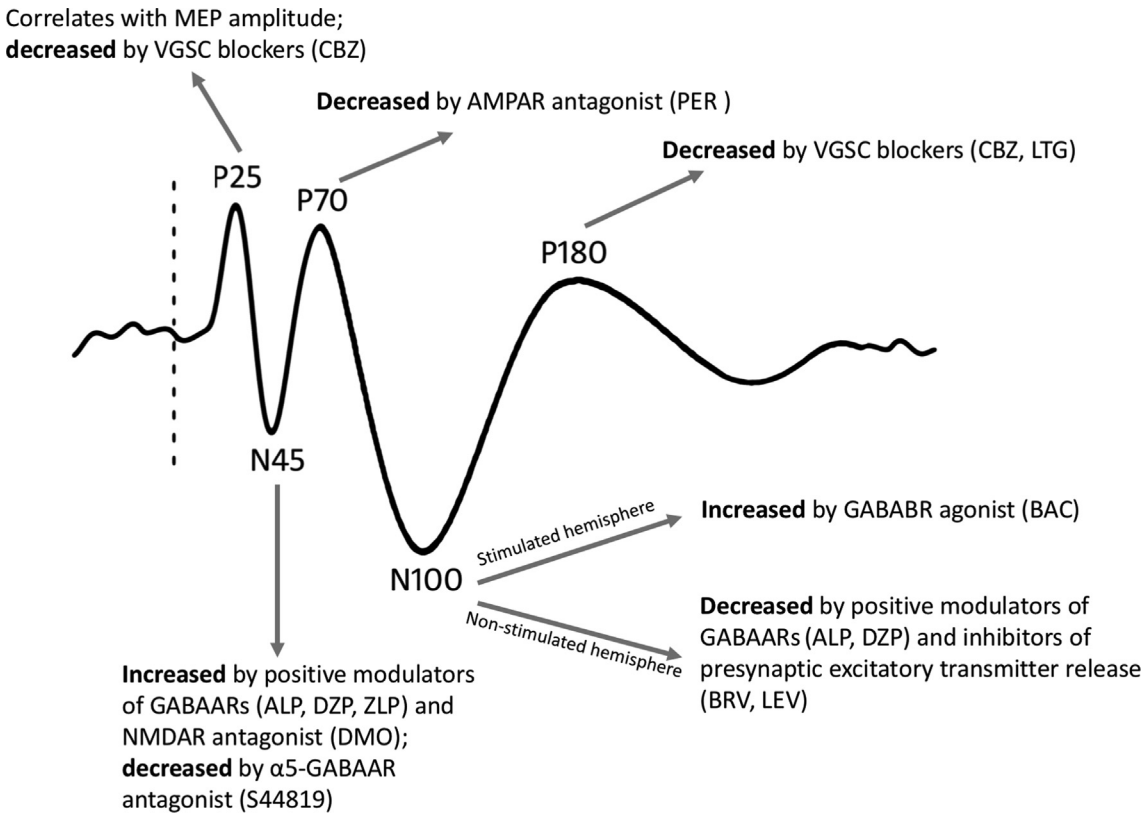

Fig. 1. Schematic of the pharmaco-physiological mechanisms of typical TEPs evoked by single-pulse TMS of M1. The dashed vertical line represents the time of the TMS pulse (time 0). ALP, alprazolam; BAC, baclofen; BRV, brivaracetam; CBZ, carbamazepine; DMO, dextromethorphan; DZP, diazepam; LTG, lamotrigine; LEV, levetiracetam; PER, perampanel; ZLP, zolpidem.

Table 1
Synopsis of pharmacological modulation of single-pulse TEP amplitude in M1.

Drug	Mode of action	Single oral dose	Modulation of single-pulse TEP amplitude					Literature
			P25	N45	P70	N100	P180	
Carbamazepine	VGSC blocker	600 mg	↓				↓	[1]
Lamotrigine	VGSC blocker	300 mg					↓	[5]
Alprazolam	GABAAR agonist	1 mg		↑		↓		[2]
Diazepam	GABAAR agonist	20 mg		↑		↓		[2]
Zolpidem	GABAAR agonist	10 mg		↑				[2]
S44819	GABAAR antagonist	100 mg		↓				[4]
Baclofen	GABABR agonist	50 mg				↑		[2]
Brivaracetam	Inhibitor of excitatory NT release	100 mg				↓		[1]
Levetiracetam	Inhibitor of excitatory NT release	3000 mg				↓		[5]
Perampanel	AMPAR antagonist	12 mg			↓			[3]
Dextromethorphan	NMDAR antagonist	120 mg		↑				[3]

Pharmacology of single-pulse TEPs outside M1

Ferrarelli and colleagues applied TMS over premotor cortex under anesthetic doses of midazolam (classical benzodiazepine) [6], and Sarasso et al. employed TMS over premotor and parietal cortex and administered anesthetic doses of ketamine (NMDAR antagonist), xenon (NMDAR antagonist and enhancer of K+ currents) and propofol (positive modulator of GABAARs) [7]. Xenon resulted in a global long-lasting cortical activation (measured with cortical current density maps), while ketamine showed a wakefulness-like TEPs pattern. Midazolam and propofol both led to high-amplitude, local and short-duration TEPs that did not propagate from the stimulation site. These results provide more evidence that positive modulators of GABAARs (propofol, midazolam, alprazolam, and diazepam) reduce long-range effective connectivity by reducing activity propagation to areas distant from the stimulation site. In contrast, the nil findings for the ketamine suggest that glutamatergic neurotransmission is less important for propagation of evoked activity measured with TEPs.

Pharmacology of double-pulse TEPs over M1

Pharmacological double-pulse TMS-EMG experiments revealed that long-interval intracortical inhibition (LICI) and short-interval intracortical inhibition (SICI) reflect inhibitory neurotransmission through GABABRs and GABAARs, respectively, because baclofen but not benzodiazepines enhanced LICI while, conversely, benzodiazepines but not baclofen enhanced SICI [8]. In contrast, baclofen enhanced both long- and short-interval double-pulse TMS-evoked inhibition of TEPs, while diazepam suppressed them

[9,10]. These findings indicate that the mechanisms of inhibition measured with TEPs evoked by double-pulse TMS over M1 are significantly different from those measured with double-pulse MEPs (such as LICI and SICI). Baclofen also increased long-interval double-pulse inhibition of TEPs over dorsolateral prefrontal cortex (DLPFC), corroborating the idea that activation of GABABRs contributes to this form of inhibition in M1 and DLPFC [11]. To what extent the pharmacophysiological characterization of TEPs, summarized here mainly for M1, will apply to TEPs elicited in other areas of the brain is currently unclear and will require experimental validation.

Conclusion

Systematic pharmacological characterization of TEPs reveals novel insights into their underlying excitatory, inhibitory and connectivity mechanisms. This knowledge is important for utilizing TEPs as surrogate markers in studies investigating brain disorders with altered cortical excitability or connectivity.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to this work.

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