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State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation

Walter Paulus, MD[a], Joseph Classen, MD[b], Leonardo G. Cohen, MD[c], Charles H. Large, PhD[d], Vincenzo Di Lazzaro, MD[e], Michael Nitsche, MD[a], Alvaro Pascual-Leone, MD, PhD[f], F. Rosenow, MD[g], John C. Rothwell, PhD[h], Ulf Ziemann, MD[i]

[a]*Department of Clinical Neurophysiology, University of Göttingen, Göttingen, Germany*
[b]*Department of Neurology, University of Wuerzburg, Wuerzburg, Germany*
[c]*Human Cortical Physiology Section and Stroke Neurorehabilitation Clinic, NINDS, National Institutes of Health, Bethesda, Maryland*
[d]*Medicines Research Centre, Glaxo Smith Kline S.p.A, Verona, Italy*
[e]*Institute of Neurology, Università Cattolica, Rome, Italy*
[f]*Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachussets*
[g]*Department of Neurology, University of Marburg, Marburg, Germany*
[h]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, England*
[i]*Department of Neurology, Goethe-University, Frankfurt am Main, Germany*

The combination of brain stimulation techniques like transcranial magnetic stimulation (TMS) with CNS active drugs in humans now offers a unique opportunity to explore the physiologic effects of these substances in vivo in the human brain. Motor threshold, motor evoked potential size, motor evoked potential intensity curves, cortical silent period, short-interval intracortical inhibition, intracortical facilitation, short-interval intracortical facilitation, long-interval intracortical inhibition and short latency afferent inhibition represent the repertoire for investigating drug effects on motor cortical excitability by TMS. Here we present an updated overview on the pharmacophysiologic mechanisms with special emphasis on methodologic pitfalls and possible future developments or requirements.

keywords transcranial magnetic stimulation; TMS; pharmacology; ICI; ICF; silent period; SAI

Noninvasive brain stimulation techniques like transcranial magnetic stimulation (TMS) offer an elegant opportunity to study mechanisms of cortical physiology at the systems level of the human brain. The combination of brain stimulation with central nervous system (CNS) active drugs might help to explore the neurophysiologic basis of specific TMS protocols on the one hand. On the other hand, TMS is an important tool to monitor the effects of these drugs on brain physiology. However, some limitations of

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pharmacologic TMS studies have to be taken into account. The effects of many drugs available for human studies are not as specific as we would like them to be. Most of the compounds tested in humans are only partially selective for the functions that are claimed in most reports.

Here we gather the currently available information about the pharmacologic influence on motor cortical excitability parameters measured by TMS. We will also discuss limitations of the approaches conducted so far, as well as debate general limitations and pitfalls of studies combining TMS with pharmacologic agents.

Acute drug intake: Effects on TMS parameters

Motor threshold

Motor threshold (MT) is a global measure of corticospinal excitability and depends on the excitability of axons activated by the TMS pulse, as well as the excitability of synaptic connections at both the cortical and spinal level. At rest, the excitability of corticomotoneuronal synapses in the spinal cord is well below firing threshold and summation of more than one descending I-wave volley is required to discharge motoneurons, leading to later motor-evoked potential (MEP) onset when relaxed than when active.[1] Because I-waves reflect synaptic activation of corticospinal neurons, it can be expected that resting motor threshold (RMT) depends on glutamatergic synaptic excitability. In contrast, during contraction, there exists always a subliminal fringe of corticospinal neurons and spinal motoneurons that are very close to firing threshold. The result is that active motor threshold (AMT) is lower than RMT, and probably depends more directly on axon threshold. In many studies this distinction has not been made and only resting threshold was investigated. This constitutes a weakness as certain drugs work specifically on sodium (Na^+) channels, whereas others affect glutamatergic synapses. However, at present there is no experimental evidence that resting and AMTs are differently affected by CNS active drugs.[2]

Voltage-gated Na+ channels are crucial in regulating axon excitability,[3] whereas ionotropic non-N-methyl-D-aspartate (NMDA) glutamate receptors are responsible for fast excitatory synaptic neurotransmission in neocortex.[4] Accordingly, drugs that block voltage-gated Na^+ channels, in particular anticonvulsants such as carbamazepine (CBZ),[2] oxcarbazepine,[5] phenytoin,[6,7] lamotrigine (LTG),[2,8-10] and losigamone[2] elevate MT (Table 1). The increase in MT correlates with the serum level of the study drug,[7,9] with quite a bit of interindividual variability.[9]

Five weeks of chronic CBZ and LTG intake in healthy subjects increase RMT and this change correlates with increasing total and free CBZ and LTG blood levels during drug administration, but no longer during drug withdrawal. After acute antiepileptic drug (AED) withdrawal, RMT elevation persisted in most individuals with CBZ despite undetectable plasma levels, compared with a rapid normalization with LTG. However, acute drug withdrawal resulted in a transient decrease in RMT in 3 of 10 individuals with CBZ and 2 of 10 with LTG.[11] Prediction of therapeutic response by drug effects on TMS measures of cortical excitability still is a vision that has never been systematically tested.

The NMDA receptor antagonist ketamine, which paradoxically increases indirectly glutamatergic neurotransmission through the non-NMDA AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, decreases MT[12] (Table 1). On the contrary, acute pharmacologic modulation of neurotransmission through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and of neuromodulating neurotransmitter systems (dopamine, DA; norepinephrine, NE; serotonin, 5-HT; acetylcholine, ACh) does not produce consistent effects on MT (Table 1).

Variability of MT is lower than that of visual phosphene thresholds.[13] Long-term stability of MT has not been formally tested. In single individuals RMT and AMT have been stable within 1% of MSO more than >10 years (U. Ziemann, personal communication). Also, dose tolerance effects have not been studied, because this would require chronic drug intake. Most of the published studies used explicitly single oral doses that were chosen to match typically used therapeutic doses.[2]

In summary, elevation of motor threshold by Na^+ channel blockers without an influence by modification of GABAergic neurotransmission still provides one the clearest concepts of a link between TMS and neuropharmacology. However, future studies might explore more systematically possible pharmacophysiologic differences between AMT and RMT, as outlined previously.

MEP amplitude

MEP amplitude increases with TMS intensity[14,15] with intrinsic variability.[16] Whether activation of the corticospinal system increases in an approximately sigmoid fashion with stimulus intensity remains to be determined, for example, by the triple-stimulation technique (TST).[16] At low stimulus intensity, the corticospinal volley resulting in the MEP often consists of only one single wave (I1-wave if the current induced by TMS in the brain runs in posterior-to-anterior direction), whereas the corticospinal volley becomes more complex and consists of multiple I-waves (I2-I4 in addition to I1) at higher stimulus intensity.[17] I1 and later I-waves have different properties. The I1-wave has the lowest threshold with the posterior-to-anterior current direction, whereas the I3-wave has the lowest threshold when the direction of the induced current in the brain is reversed.[17,18] Further differences between I-waves are constituted by their different sensitivity to lorazepam administration and by their different behavior in several TMS protocols testing intracortical inhibition.[17] Some