Single pulse TMS, paired TMS and repetitive TMS: Mechanisms of action

Yoshikazu Ugawa
Department of Neurology, Fukushima Medical University
ugawa-tky@umin.net

What’s TMS?
• Induced currents activates neurons.
• Human brain can be activated non-invasively.

Transcranial magnetic stimulation

1. Single pulse TMS
   - Induced currents activates neurons (electric stimulation)
   - Human brain can be activated non-invasively.

2. Repetitive TMS: rTMS
   - After rTMS, long lasting MEP changes occurs, reflecting with cortical excitability changes.

Currents induced in the brain by the magnetic field changes produced by huge currents in the coil electrically activate neurons (electric stimulation)
Today’s Talk

1. What are stimulated by single pulse TMS?

2. To study modulation effects on M1, cerebellum, sensory inputs and others

3. What happens after repetitive TMS?

MEP and CMAP

- Spinal motoneuron
- Cortical latency
- Several kinds
- One axon
- NMJ

Difference of cortical latency by TMS and TES

Muscle evoked potentials (MEP) of the first dorsalis interosseous muscle (FDI)

The cortical latency of MEP to TMS is about 1.5ms longer than that to TES.

Multiple descending volleys

TMS induces multiple descending volleys (I1, I2, I3 waves) at about 1.5ms intervals. The latency of I1 wave is later than D-wave (direct wave) induced by TES.
Hypothesis for generator of I-waves

Multiple descending volleys

Induced currents

I-waves are probably induced trans-synaptically in the M1.

The primary motor cortex (M1)

However, the pyramidal neurons are not positioned in the bank of the precentral gyrus, but in anterior wall of the central sulcus (area 4).

Today's Talk

1. What are stimulated by single pulse TMS?
2. To study modulation effects on M1. cerebellum, sensory inputs and others
3. What happens after repetitive TMS?
Randomized conditioning-test paradigm

Stimulation
- conditioning stimulus: cerebellar stimulation (ES or TMS)
- test stimulus: TMS over M1

EMG recording
- surface EMG from the FDI

Interstimulus intervals
- 3 – 10 ms

Analysis
- comparison between control and conditioned trials

Characteristics of the suppression

Conditioning stimulus suppresses EMG responses to TMS over the motor cortex, whereas it does not affect those to electrical stimulation over M1. Effects should occur at the cortex.

Position and polarity of effective conditioning stimulus suggests that conditioning stimulus should be over the cerebellum contralateral to the motor cortex.

Cerebellar effect?
Motor cortical suppression by cerebellar stimulation in patients

Reduced suppression (abnormal)
- cerebellar hemispheric lesion (CCA, paraneoplastic synd CVD, DPH intoxication)
- cerebellar efferent system (sup cbl peduncle lesion, dentate, motor thalamus)
- degenerative ataxia

Normal suppression with ataxia
- cerebellar afferent system (pontine nucl, middle cerebellar peduncle)
- sensory ataxia (neuropathy, tabes dorsalis sensory thalamic lesion)
- Fisher’s syndrome hypothyroidism

Summary of the results
- Normal cerebellar inhibition
  - Non-cerebellar ataxia
    - sensory ataxia
    - Fisher’s syndrome
    - hypothyroidism
- Cerebellar ataxia
  - Cerebellar afferent pathway
    - frontal ataxia, pontine nucleus middle cerebellar peduncle
  - Abnormal cerebellar inhibition
    - Cerebellar hemispheric dysfunction
    - Cerebellar efferent pathway
      - superior cerebellar peduncle motor thalamus thalamo-M1 fibers

Simple interpretation of mechanism for cerebellar suppression
- TMS activates Purkinje cells (near to coil)
- Purkinje cells inhibit dentate nucleus which tonically activates M1 through dentate-thalamo-cortical pathway
- M1 background activity is suppressed by disfacilitation
- Cerebellar afferent pathways have no contribution to cerebellar suppression

Today’s Talk
1. What are stimulated by single pulse TMS?
2. To study modulation effects on M1 cerebellum, sensory inputs and others
3. What happens after repetitive TMS?
repetitive TMS

Quadri-pulse stimulation: QPS

Four pulses of monophasic TMS are applied every 5 sec for 30 minutes (360 burst) over M1

Short-intervals
QPS at
5 sec

1.5, 5, 10 ms

Long-intervals
QPS at
5 sec

30, 50, 100, 1250 ms

Aftereffects of QPS depends on inter-stimulus intervals of 4 pulses

Short-interval QPS induce LTP like effects

Long-interval QPS induce LTD like effects

QPS and BCM curve

MEP ratio at 30min after QPS to pre-QPS

LTP/LTD like effects after QPS seems to follow BCM theory.
Conclusion

- NIBS activates inter-neurons and inputs fibers in M1.
- Preferentially activated components by NIBS depends on stimulus intensity or current directions.
- MEPs to NBS reflects the combination of all synaptic changes in M1. Each NIBS may have its specific combination of several synapses.