Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning

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History of tDCS

- Discovered in early 1800s, clinical experimentation by Giovanni Aldini (Horvath JC, 2010)
- 1930s: tDCS was abandoned as other forms of neurostimulation were thought to have more potential (Utz et al. 2010)
- 1960s: discovery that tDCS has an effect on cortical excitability (Utz et al. 2010)
- Current research: tDCS is better understood now, with better imaging and stimulation techniques (Nitsche et al. 2008)

Reasons behind current study of tDCS

- Non-invasive, lost cost, easy to use (Utz et al. 2010).
- Positive effects seen in motor, visual, somatosensory, attentional, vestibular and emotional functioning regions of brain (Utz et al. 2010).
- Can be used to boost recovery after stroke by enhancing new connections (Singer E, 2009).

Methods and Results Part I

Rat brain slice preps, primary motor cortex (M1)
Coupling of low-frequency synaptic activation (LFS) with transcranial direct current stimulation (tDCS)

- Recorded amplitude of fEPSPs (field excitatory post-synaptic potentials) in motor cortex of rats
- 15 mins of 0.75 mV anodal DCS, with 0.1 Hz LFS
- Showed long-term potentiation (LTP) in EPSPs that lasted for at least 2 hours.
Summary Part I

- tDCS coupled with LFS in rat M1 slices causes long-term potentiation
- LTP endures long after DCS is stopped, for at least 2 hours
- NEXT: could this be related to NMDA receptors?

NMDA receptors

- \( N-methyl D-aspartate \)
- Type of glutamate receptor
- Non-specific cation channel: allows \( Ca^{2+}, Na^+ \) and \( K^+ \) currents to flow
- Ligand-gated and voltage gated
- Implicated in synaptic plasticity, such as LTP

Methods and Results Part II

- Added NMDA antagonist (D-APV) to see if this stops LTP from occurring
- NMDA antagonist prevents potentiation, supports hypothesis that DCS is NMDA-dependent

Summary Part II

- tDCS coupled with LFS in M1 of rat brain slices causes NMDA-dependent long-term potentiation
- This is NOT due to disinhibition of GABA
- NEXT: Investigating the role that the neurotrophic factor BDNF has on NMDA-dependent potentiation
Neurotrophins

- Proteins / growth factors that promote the survival and development of neurons
- BDNF: Brain-derived neurotrophic factor, secretion depends on calcium and NMDA activation (Balkowiec and Katz, 2002)

(Krizkova A, 2009)

Methods and Results Part III

- 1) BDNF<sup>flox/flox, cre</sup>: knockout mice with a forebrain-specific deletion of the BDNF gene.
  - + Cre: absence of BDNF
  - - Cre: control
- BDNF knockouts with Cre+ do not show potentiation
- 2) Used TrkB-IgG to diminish BDNF present in the cortex: this also inhibits potentiation

Fritsch et al. (2010), fig. 2A

Method and Results Part III

- Possible role of TrkB (BDNF receptor)?
- TrkB<sup>F616A</sup> knock-in mice: allows for selective inhibition of receptor kinase activity of TrkB receptor by the molecule 1NMPP1

Fritsch et al. (2010), fig. 2B

C

Fritsch et al. (2010), fig. 2C
Methods and Results Part III

• Does DCS increase secretion of BDNF?
• Method: western blotting with antibodies against phospho-TrkB and total TrkB.
• Check for TrkB levels before and after DCS
• Result: DCS increases BDNF levels over two-fold

Summary Part III

• tDCS and LFS induces NDMA-dependent, BDNF-dependent long-term potentiation
• TrkB (BDNF receptor) is important for LTP induction
• DCS/LFS increases BDNF secretion in the brain
• FINALLY: How does this relate to human motor learning?

Methods and Results Part IV

• Motor skill acquisition tests in humans: sequential visual isometric pinch force task.
• Studied humans with BDNF Val66Met polymorphism:
  – Val/Val: control
  – Met carriers: 18-30% reduction in BDNF

Fritsch et al. (2010), fig. 2D
Fritsch et al. (2010), fig. S3A,B
Fritsch et al. (2010), fig. 3A
Methods and Results Part IV

- Compared human and mouse motor acquisition tasks
- BDNF knock-in mice: accelerating rotarod task
  - Mice:
    - Wild type: normal BDNF levels
    - BDNF<sup>Met/Met</sup>: reduces activity-dependent BDNF by 30%
    - BDNF<sup>flox/flox</sup>, cre: BDNF is absent

The Accelerating Rotarod Test

![Accelerating Rotarod Test](image_url)

![Graphs](image_url)
Overall conclusions

• Anodal DCS / LFS in M1 induces LTP that requires activity-dependent BDNF
• Does DCS/LFS trigger the release of proBDNF?
• Factors other than BDNF still must be considered:
  • Possible involvement of spike-timing dependent plasticity
• Future work must be done, exploring effects of other molecules and neuromodulators

Future of tDCS

• Can be used in vitro to induce plasticity
• Implications in treatment of neurodegenerative disorders — neurorehabilitation.

References


Singer, E (2009)