Neuroscience 278 (2014) 93–104

NEUROSCIENCE FOREFRONT REVIEW

THE ROLE OF INHIBITION IN HUMAN MOTOR CORTICAL PLASTICITY

V. BACHTIAR AND C. J. STAGG *

Oxford Centre for Functional MRI of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Abstract—Over recent years evidence from animal studies strongly suggests that a decrease in local inhibitory signaling is necessary for synaptic plasticity to occur. However, the role of GABAergic modulation in human motor plasticity is less well understood. Here, we summarize the techniques available to quantify GABA in humans, before reviewing the existing evidence for the role of inhibitory signaling in human motor plasticity. We discuss a number of important outstanding questions that remain before the role of GABAergic modulation in long-term plasticity in humans, such as that underpinning recovery after stroke, can be established.

Key words: GABA, motor, plasticity, stroke recovery, human.

Contents

Introduction 93
Quantifying GABA in humans *in vivo* 94
A brief overview of GABA metabolism and signaling in the adult human brain 94
Measurement of GABA in the resting brain 95
MRS 95
TMS 96
Measures of GABAergic activity during movement 97
Changes in GABAergic signaling with aging 97
GABA modulation is demonstrated during plasticity in healthy adults 97
GABA decreases occur in response to a wide range of plasticity-induction protocols 97
NIBS 98
Can GABA decreases be related directly to learning of a motor task? 98
Do NIBS protocols that modulate GABA levels also modulate learning rates? 98
GABAergic synapses as a site for homeostatic plasticity 99
A role for GABA in long-term plasticity? 100
Future directions 101
Is GABA modulation *necessary* for short-term plasticity induction? 101
A role for GABA modulation in the chronic stage of stroke recovery? 101
Functionally-relevant modulation of GABA 101
Exploring the physiological underpinnings of the MRS-assessed GABA signal – the necessity for multimodal approaches 101
M1 as part of a wider functional network 102
Conclusions 102
Acknowledgments 102
References 102

INTRODUCTION

Plasticity can be loosely defined as the ability of the brain to adapt to respond to new challenges. In humans, plasticity occurs largely through modification of the strength of synaptic connections. This flexibility in behavior can be demonstrated in the learning of a new motor task or recovery of motor function after a stroke, but can also be induced non-invasively via transcranial stimulation techniques such as transcranial direct current stimulation (tDCS).

Synaptic plasticity was described as follows in Hebb's seminal 1949 work: "*When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells, such that A's efficiency, as one of the cells firing B, is increased*" (Hebb, 1949). Synaptic plasticity encompasses a number of pre-synaptic and post-synaptic changes, the most ubiquitous of which is Long-Term Potentiation (LTP)-like plasticity.

LTP-like plasticity is demonstrated as the rapid and sustained increase of strength of glutamatergic synapses. The details of glutamatergic LTP and LTP-like plasticity are increasingly well understood, but their complexity falls outside the scope of this review (see for example, Feldman, 2009 for a review). There is increasing evidence emerging from both animal models

*Corresponding author. Address: FMRIB, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK. Tel: +44-(0)1865-222736; fax: +44-(0)1865-222717.
E-mail address: charlotte.stagg@ndcn.ox.ac.uk (C. J. Stagg).

Abbreviations: BCM, Bienenstock–Cooper–Munro; CS, conditioned stimulus; cTBS, continuous theta-burst stimulation; EMG, electromyography; fMRI, functional MRI; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; ISI, inter-stimulus interval; iTBS, intermittent theta-burst stimulation; LICI, Long-Interval Intracortical Inhibition; LTD, Long-Term Depression; LTP, Long-Term Potentiation; M1, primary motor cortex; MEG, magnetoencephalography; MRS, Magnetic Resonance Spectroscopy; NIBS, non-invasive brain stimulation; ppTMS, paired-pulse TMS; SICI, short-interval intracortical inhibition; TBS, theta-burst stimulation; tDCS, transcranial direct current stimulation; TMS, Transcranial Magnetic Stimulation.

http://dx.doi.org/10.1016/j.neuroscience.2014.07.059
0306-4522/

and human studies that an initial decrease in local γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the adult mammalian brain, is of vital importance for allowing LTP-like plasticity to occur (Castro-Alamancos et al., 1995; Trepel and Racine, 2000; Clarkson et al., 2010).

Here, we review the evidence for GABA modulation in human motor plasticity, both during the learning of new motor skills in healthy controls and in the recovery of motor function after stroke, two processes that have many similarities (Krakauer, 2006). We focus on changes occurring within the primary motor cortex (M1) during the learning of motor skills as this is the region that has been studied in most depth.

We first review the methods by which inhibitory signaling can be quantified in humans, and the relative advantages and disadvantages of each of these techniques. We then go on to discuss the emerging literature highlighting the role of GABAergic modulation in plasticity in healthy subjects. Finally, we review the current evidence for the role of GABA in recovery of function after a brain injury such as a stroke.

QUANTIFYING GABA IN HUMANS *IN VIVO*

The role of GABA in the induction of LTP-like processes that underpin neuroplastic mechanisms in animal models is well established (Castro-Alamancos et al., 1995; Sanes and Donoghue, 2000; Trepel and Racine, 2000; Clarkson et al., 2010). However, in the adult human brain, GABA is present at millimolar levels, which has historically made it difficult to quantify. Nevertheless, recent technical and methodological advances in Magnetic Resonance Spectroscopy (MRS) and non-invasive brain stimulation (NIBS) approaches have made reliable quantification of GABA more achievable. In turn, the ability to accurately measure inhibitory signaling has sparked increased interest in understanding the role of GABA both in motor learning in healthy controls and in recovery of motor function after stroke.

In addition to MRS, other imaging methods have been shown to be able to evaluate inhibitory activity. Positron Emission Tomography (PET) is increasingly being used to quantify GABAergic activity, with specific ligands being developed for specific GABA receptors (see Andersson and Halldin, 2013 for a full review and comprehensive summary of available compounds). Other techniques are also available to assess inhibitory activity, albeit indirectly. For example, magnetoencephalography (MEG) allows for the non-invasive measurement of neuronal network oscillations in the beta-frequency range (15–30 Hz), and gamma-frequency range (30–100 Hz), both of which are thought to be under the direct control of GABAergic modulation (Bartos et al., 2007). Others have shown the potential effect of excitation-inhibition changes on hemodynamic responses as measured by BOLD functional MRI (fMRI) (Logothetis, 2008). However, a full discussion of these methods is beyond the scope of this review.

A brief overview of GABA metabolism and signaling in the adult human brain

GABA is the primary inhibitory neurotransmitter in the central nervous system and is primarily metabolized from glutamate via the enzyme glutamic acid decarboxylase (GAD), found within GABAergic neurons. In humans, GAD is found in two distinct forms with molecular weights of 65 and 67 kDa (given the nomenclature GAD_{65} and GAD_{67} respectively). GABA is found in two distinct functional pools within inhibitory neurons, each of which appear to be regulated by a distinct form of GAD. The majority of GABA is found in the cytosol and is regulated by the tonically active GAD_{67} (Martin and Rimvall, 1993) and does not appear to contribute significantly to GABAergic neurotransmission (Wei et al., 2004; Wei and Wu, 2008). GABA is also found at high concentrations in a vesicular pool in the presynaptic boutons, the production of which is regulated by the phasically active GAD_{65} (Martin and Barke, 1998). Vesicular GABA has a key role in inhibitory synaptic neurotransmission (Martin and Rimvall, 1993) and GAD_{67} has been shown to have an activity-dependent role in GABA synthesis such that decreased network activity leads to decreased expression of GAD_{67}, which in turn leads to lower vesicular filling of the transmitter and thus GABA levels (Lau and Murthy, 2012).

After release from the GABAergic neuron, the vast majority of GABA is metabolized to succinic acid semialdehyde in the GABAergic interneurons and surrounding astrocytes by GABA transaminase (GABA-T) (Petroff and Rothman, 1998).

As a neurotransmitter GABA acts on two major families of post-synaptic GABA receptors. $GABA_A$

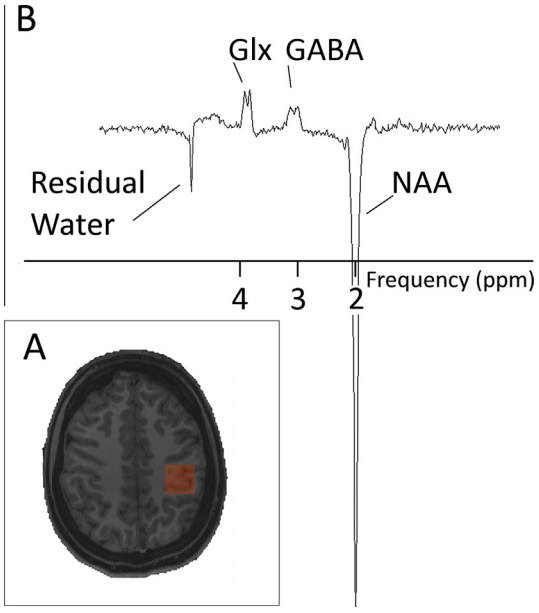

Fig. 1. Typical GABA-edited MRS spectrum. (A) A typical voxel location for a 2 × 2 × 2 cm left M1 voxel. (B) A typical GABA-edited MEGA-PRESS spectrum acquired from the voxel illustrated in A. Representative peaks from GABA, Glx (a composite measure of glutamate and glutamine) and NAA are visible.