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Perspective

Mechanisms of motor learning mediated by synaptic plasticity in rat primary motor cortex

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ABSTRACT

Motor skill training induces long-term potentiation (LTP) and structural plasticity at dendritic spines in the primary motor cortex (M1). However, little is known about the plasticity of individual M1 neurons. Skilled motor coordination in rodents was recently assessed in studies using an accelerated rotor rod task with 1–2 days of training. Using this model, we investigated the effects of motor training on both AMPA receptor-mediated excitatory synapses and $GABA_A$ receptor-mediated inhibitory synapses in layer II/III neurons in the M1. One day of the motor training strengthened AMPA receptor-mediated excitatory synapses and drastically reduced presynaptic GABA release probability. Two days of the training further strengthened AMPA receptor-mediated excitatory synapses as well as NMDA receptors, and increased presynaptic glutamate release while also restoring presynaptic GABA release probability. In this review, we discuss the dynamic changes observed in both glutamatergic and GABAergic plasticity as well as intrinsic plasticity after the training.

Contents

1. Introduction

Fine motor skills improve with training. The primary motor cortex (M1) is traditionally considered to be an output area responsible for skilled voluntary movements (Evarts, 1968). M1 neurons form a well characterized glutamatergic/GABAergic neural circuit, and motor experience can alter spine morphology and efficacy of synaptic transmission (Rioult-Pedotti et al., 2000; Rioult-Pedotti et al., 1998; Xu et al., 2009; Yang et al., 2009). While previous studies have reported changes in synaptic strength following motor training, the mechanism underlying these changes at excitatory synapses remains unclear and the role of GABA neurotransmission at inhibitory synapses is completely unknown. Additionally, changes in intrinsic properties, such as resting membrane potential and spike frequency, are not well characterized.

Kida et al. recently demonstrated that motor training promotes synaptic plasticity at both excitatory and inhibitory synapses (Kida et al., 2016), indicating that this plasticity in M1 is dependent on motor learning. In this review, we discuss observations indicating that two days of training on an accelerated rotor rod task promotes dynamic changes in glutamatergic and GABAergic properties and intrinsic plasticity at layer II/III neurons in M1. These results pro-

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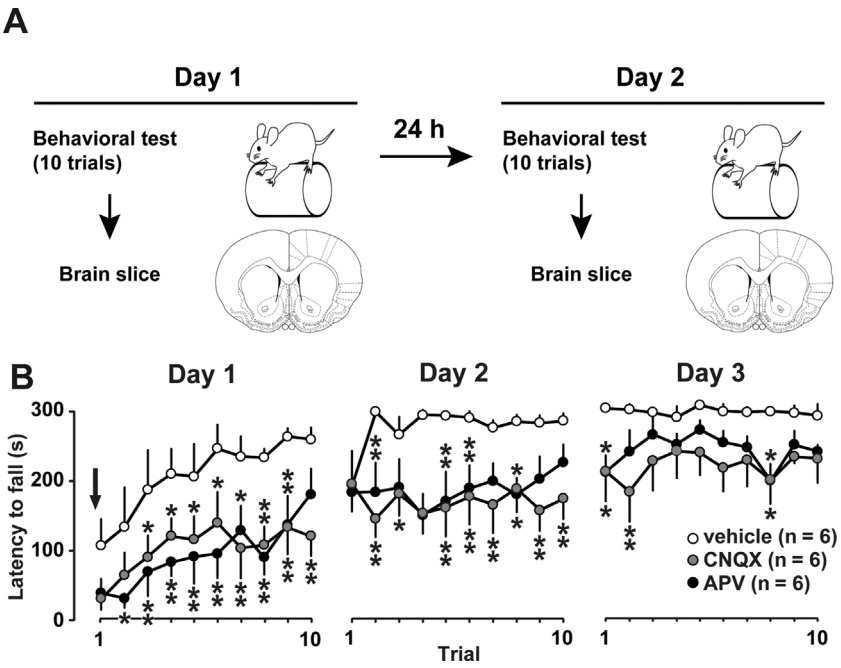

Fig. 1. (A) The design of the rotor rod training and coronal brain slice experiments. (B) Mean latency to fall from the barrel plotted for each trial (10 trials/day). Vehicle, CNQX, or APV was bilaterally microinjected into the M1 before the first trial. Arrows indicate microinjection timing. The number of rats in each group is shown in parentheses. *P < 0.05, **P < 0.01 vs. vehicle. Error bars indicate ± SEM. (Kida et al., 2016).

vide functional evidence for the structural remodeling of dendritic spines after motor skill training.

2. Motor learning test

We conducted a rotor rod test to evaluate changes in motor skills in 4-week-old rats. Rats were assigned to either the naive group (untrained), a one day training group (1-day trained), or a two-day training group, in which motor training occurred on two successive days (2 days trained) (Fig. 1A). The rats were allowed 10 attempts with a 30 s inter-trial interval for each test. The rotor rod was set to increase from 4 rpm to 40 rpm over 5 min, and the duration of rod-riding was recorded. We recorded the average latency to falling from the rotating rod, and considered longer latency as indicative of better motor performance. Rats clearly improved their motor performance from their first to last trial on the first training day. Their performance reached nearly asymptotic levels on the second training day, indicating that two days of training was sufficient for motor skill acquisition. This behavioral paradigm could be useful for investigations of neural mechanisms underlying many diverse behavioral phenomena, such as anti-depressive and/or anti-anxiety behavior.

3. Role of glutamatergic transmission in the M1

Activation of AMPA-type glutamate receptors induces fast excitatory neurotransmission that facilitates memory and task-related behavior enhancement. NMDA receptor activation is implicated in the maintenance of spatial memory as well as associative learning (Riedel et al., 2003). Prior to the first training, we performed bilateral microinjection of either the AMPA receptor antagonist CNQX (1 μg/μL, per side), the NMDA receptor antagonist APV (1 μg/μL, per side), or vehicle (13% DMSO, 1 μL, per side) was bilaterally microinjected into the M1 to investigate the role of glutamatergic transmission on behavioral performance. Bilateral microinjection of either APV or CNQX prior to motor skill acquisition impaired motor performance relative to vehicle injected controls (Fig. 1B), suggesting that both NMDA and AMPA receptors are required for motor skill acquisition. Since the transient effect of CNQX did not affect open field performance, it is possible that AMPA receptor-mediated glutamatergic transmission is closely associated with the acquired motor skill rather than basic motor activity in M1.

CNQX microinjections prior to motor training resulted in longer lasting effects on motor learning, while microinjections following training transiently attenuated performance (Kida et al., 2016). These findings inspired the hypothesis that microinjections of CNQX or APV before training could block calcium triggered plasticity and learning, while activated postsynaptic AMPA receptor turnover after training might shorten the observed effect of CNQX. Additional studies are necessary to compare AMPA receptor recycling and insertion of AMPA receptors before and after motor training to confirm this hypothesis.

4. Glutamatergic plasticity

Previous studies indicate that forelimb motor training strengthens horizontal connections in M1 layer II/III (Rioult-Pedotti et al., 2000). Motor training is known to induce LTP in M1 layer II/III neurons, but the detailed mechanisms of plasticity at the synapse level are not well understood. To investigate this phenomenon, we analyzed synaptic plasticity in layer II/III neurons using the voltage clamp technique in the cortical slice of M1. We electrically stimulated horizontal connections to evoke EPSCs in layer II/III neurons, and calculated the AMPA/NMDA ratio as the ratio of the peak current measured at −60 mV to the current measured at +40 mV, 150 ms after stimulus onset (Kida et al., 2016). We found a significant increase in AMPA/NMDA ratio in 1-day trained rats compared to untrained rats. We also recorded miniature EPSCs (mEPSCs) in the presence of 0.5 μM tetrodotoxin (Fig. 2A) at −60 mV. 1-day trained rats exhibited a significant increase in mEPSC amplitude only, while 2 days trained rats exhibited significant increases in both mEPSC amplitude and frequency (Fig. 2B). A previous study suggested that phosphorylation of the AMPA receptor GluA1 subunit at Ser^{831} is required for receptor trafficking into

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