

METAPLASTIC UP-REGULATION OF LTP IN THE RAT VISUAL CORTEX BY MONOCULAR VISUAL TRAINING: REQUIREMENT OF TASK MASTERY, HEMISPHERIC SPECIFICITY, AND NMDA–GLUN2B INVOLVEMENT

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Abstract—“Metaplasticity” is defined as an alteration of synaptic plasticity properties or mechanisms by a priming event without actual changes in synaptic strength. For example, visual discrimination training of rats leads to a facilitation of the subsequent induction of long-term potentiation (LTP) between the lateral geniculate nucleus (LGN) and the primary visual cortex (V1). Here, rats received visual discrimination training in a modified water maze, with one eye occluded during training to create monocular viewing conditions; 63% of rats acquired the task under these conditions. Following training, *in vivo* electrophysiology was used to examine LTP of field postsynaptic potentials (fPSPs) in V1 elicited by LGN stimulation. Rats that had successfully learned the task showed significantly greater LTP in the “trained V1” (contralateral to the open, trained eye) relative to the “untrained” hemisphere. Rats that underwent training but failed to acquire the task did not show this lateralized plasticity enhancement and had similar levels of LTP in both cerebral hemispheres. Cortical application of the NMDA receptor–GluN2B subunit antagonist Ro 25-6981 (2 mM) reversed the training-induced LTP facilitation without affecting LTP in the untrained V1. Whole-cell patch clamp recordings of V1 (layers II/III) pyramidal cells *in vitro* demonstrated that pharmacologically isolated NMDA

currents exhibit a greater sensitivity to GluN2B blockade in the trained relative to the untrained V1. Together, these experiments reveal a surprising degree of anatomical (only in the hemisphere contralateral to the trained eye) and behavioral specificity (only in rats that mastered the task) for the effect of visual training to enhance LTP in V1. Further, cortical GluN2B subunits appear to be directly involved in this metaplastic facilitation of thalamocortical plasticity, suggesting that NMDA subunit composition or functioning is, at least in part, regulated by the exposure to behaviorally significant stimuli in an animal's sensory environment. © 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: visual learning, visual cortex, long-term potentiation, NMDA receptor, GluN2B subunits, metaplasticity.

INTRODUCTION

Long-term potentiation (LTP) constitutes a synaptic plasticity mechanism thought to mediate the encoding and storage of new information in the adult nervous system (Martin and Morris, 2002). A number of studies have shown that various learning experiences (e.g., fear conditioning, motor, perceptual, and passive avoidance training) result in increases in synaptic strength at specific sets of synapses (Rogan et al., 1997; Rioult-Pedotti et al., 2000; Monfils and Teskey, 2004; Whitlock et al., 2006; Sale et al., 2011). Importantly, this training-induced synaptic potentiation often competes with, or occludes the subsequent induction of LTP induced by high-frequency electrical stimulation (Rioult-Pedotti et al., 2000; Monfils and Teskey, 2004; Whitlock et al., 2006), an observation that is consistent with the notion that learning and LTP share common cellular and molecular mechanisms (Martin and Morris, 2002).

Interestingly, other investigations have shown that behavioral experiences may also facilitate subsequent LTP induction, rather than lead to the occlusion effect noted above. For example, housing adult rodents in an enriched environment enhances LTP induction in the primary visual cortex (V1; Sale et al., 2007; Mainardi et al., 2010), while sound discrimination training has been shown to result in greater LTP in the primary auditory cortex of adult rats (Zhang et al., 2013). Similar to the latter observation, visual discrimination training leads to a

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Abbreviations: aCSF, artificial cerebrospinal fluid; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; CSD, current source density; EPSC, excitatory postsynaptic current; fPSP, field postsynaptic potential; IO curve, input–output curve; ISI, inter-stimulus interval; LGN, lateral geniculate nucleus; LR, learning rats; LTP, long-term potentiation; NLR, no learning rats; NMDA, N-methyl-D-aspartate; P+, presence of platform; P–, absence of platform; PP, paired-pulse; PPF, paired-pulse facilitation; PPR, paired-pulse ratio; PPS, paired-pulse stimulation; S.E.D., standard error of the difference; S.E.M., standard error of the mean; TBS, theta-burst stimulation; V1, primary visual cortex.

facilitation of LTP in the thalamocortical visual system between the lateral geniculate nucleus (LGN) and V1 of adult rats (Hager and Dringenberg, 2010), an effect that appears to involve the GluN2B subunit of N-methyl-D-aspartate (NMDA) receptors in V1 (Gagolewicz and Dringenberg, 2011). Together, the studies summarized above clearly emphasize that behavioral experience can exert complex, multi-directional effect on plasticity mechanisms, with occlusion or facilitation of LTP as possible outcomes. It is also noteworthy that effects of behavioral training on plasticity mechanisms in primary sensory cortices are not limited to perceptual tasks, but extend to discrimination and other, associative learning tasks, confirming that the primary sensory fields of the cerebral cortex can participate in a number of sophisticated, cognitive processes and behaviors (Rutkowski and Weinberger, 2005; Shuler and Bear, 2006; Weinberger, 2007; Padmala and Pessoa, 2008; Ester et al., 2009).

Alterations in plasticity induction by behavioral training may be caused by several factors, including both task-specific and other, more general influences. For example, training in sensory discrimination tasks often involves modality-specific sensory stimulation, motor activity, experience of reward contingencies, and increased levels of attention, stress and arousal, all of which could influence plasticity mechanisms throughout the forebrain. Thus, a major challenge is the dissociation of learning-specific and more general factors, all of which may contribute to alterations in brain plasticity. In this regard, a particularly elegant approach lies in the comparison of the two cerebral hemispheres of the same animal when specific sensory stimulation is restricted or preferentially directed to only one hemisphere (e.g., Chang and Greenough, 1982).

The rodent visual system displays a high degree of anatomical lateralization, with more than 90% of retinal ganglion axons of one eye innervating the contralateral LGN and V1 (Cowey and Perry, 1979; Sefton et al., 2004). Thus, under conditions of monocular occlusion, the V1 contralateral to the open eye receives more direct visual input than the ipsilateral V1, creating preferentially “viewing” and “non-viewing” hemispheres. It is important to note, however, that there is a large, anatomical area of V1 that receives binocular stimulation (the binocular zone of V1) by means of converging, crossed and uncrossed inputs from the two eyes (Sefton et al., 2004; Hofer et al., 2006; Coleman et al., 2009; Faguet et al., 2009). This anatomical arrangement, together with the fact that the weak, ipsilateral eye input to the binocular V1 exhibits considerable amplification at the level of the LGN (Coleman et al., 2009), clearly indicates that both eyes have access to either cerebral hemisphere. Thus, the terms “viewing” and “non-viewing” hemispheres/V1, as used in the present paper, imply a preferential, but not an exclusive dominance of visual information that reaches the cortex from the contralateral eye.

With the experiments described here, we assessed the effects of visual discrimination training under monocular viewing conditions on LTP induction *in vivo* between LGN and V1 of adult rats. As mentioned, previous work has showed that discrimination training

results in a facilitation of LTP in this projection system (Hager and Dringenberg, 2010). Here, by directly comparing LTP (as well as other electrophysiological parameters) in the preferentially “viewing” and “non-viewing” LGN–V1 systems, we assessed the contributions of direct visual input vs. more general, non-visual effects on the LTP enhancements seen in previous work. Additional experiments using both *in vivo* methodologies and *in vitro* whole-cell, patch-clamping techniques were designed to further probe the role of NMDA receptor subunits in the plasticity modulation seen following visual discrimination training.

EXPERIMENTAL PROCEDURES

Subjects

Experimental procedures were conducted on adult (300–650 g), male Long–Evans rats (Charles River Laboratories, Inc. Saint-Constant, Quebec, Canada). Animals were singly housed in a colony room (12/12 h reversed light cycle; light off at 7:00 h) with *ad libitum* access to food and water. All behavioral tests and electrophysiological procedures took place during the day (dark cycle), typically between the time of 9:00 and 18:00 h. Experiments were conducted in accordance with published guidelines of the Canadian Council on Animal Care and approved by the Queen’s University Animal Care Committee.

Visual discrimination training

Behavioral training was conducted in a modified water maze containing a Y-maze insert. The water maze consisted of a circular pool (180 cm in diameter, and 60 cm in height, filled with water to a height of 40 cm). The water was maintained at a temperature of 22 ± 1 °C, and rendered opaque by the addition of white, non-toxic paint. The pool contained a clear Plexiglas Y-maze insert (height, 60 cm; length, 140 cm; width, 50 cm at the proximal release site and 80 cm at the distal goal arms), which was kept in the same position throughout the entire training period. A black Plexiglas divider (height, 50 cm; length, 60 cm) separated the two goal arms. A clear Plexiglas rectangular escape platform (height, 38 cm; length, 36 cm; width, 12 cm) was placed 10 cm from the end of one of the goal arms, 2 cm below the water surface. The water opacity ensured that the platform was not visible.

Two distinct visual cues were used for discrimination training. Cues were printed on white sheets of paper (21.5 × 28 cm), and consisted of either three black, horizontal bars (length, 15 cm; width, 3 cm; spaced 3 cm apart) or three vertical bars (same dimensions and spacing as above). The visual cues were mounted at the end of the two Y-maze goal arms 1 cm above the water line.

Training of the majority of rats was carried out using a harness-facemask device (Hager and Dringenberg, 2012) to restrict visual input to one eye (monocular viewing condition). Prior to training, rats were handled and habituated

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