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Review

Functional basis of associative learning and their relationships with long-term potentiation evoked in the involved neural circuits: Lessons from studies in behaving mammals

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ABSTRACT

While contemporary neuroscience is paying increasing attention to subcellular and molecular events and other intracellular phenomena underlying the acquisition, storage, and retrieval of newly acquired motor and cognitive abilities, parallel attention should be paid to the study of the electrophysiological phenomena taking place at selected cortical and subcortical neuronal and synaptic sites during the precise moment of learning acquisition, extinction, and recall. These in vivo approaches to the study of learning and memory processes will allow the proper integration of the important information collected from in vitro and delayed molecular studies. Here, we summarize studies in behaving mammals carried out in our laboratory during the past ten years on the relationships between experimentally evoked long-term potentiation (LTP) and activity-dependent changes in synaptic strength taking place in hippocampal, prefrontal and related cortical and subcortical circuits during the acquisition of classical eyeblink conditioning or operant learning tasks. These studies suggest that different hippocampal synapses are selectively modified in strength during the acquisition of classical, but not instrumental, learning tasks. In contrast, selected prefrontal and striatum synapses are more directly modified by operant conditioning. These studies also show that besides *N*-methyl-D-aspartate (NMDA) receptors, many other neurotransmitter, intracellular mediating, and transcription factors participate in these two types of associative learning. Although experimentally evoked LTP seems to prevent the acquisition of classical eyeblink conditioning when induced at selected hippocampal synapses, it proved to be ineffective in preventing the acquisition of operant conditioned tasks when induced at numerous hippocampal, prefrontal, and striatal sites. The differential roles of these cortical structures during these two types of associative learning are discussed, and a diagrammatic representation of their respective functions is presented.

1. Introduction

It is generally assumed that learning and memory are registered and stored in the form of functional and structural changes in synaptic efficiency (Bliss & Collingridge, 1993; Hebb, 1949; Lynch, 2004; Malenka & Nicoll, 1999; Marr, 1971). There are many excellent studies in vitro studies on the subcellular and molecular events underlying learning-dependent changes in synaptic strength, as well as on the electrophysiological processes feasibly related to the acquisition of new motor and cognitive skills (Bliss & Collingridge, 1993; Engert & Bonhoeffer, 1999; Lynch, 2004; Malenka & Nicoll, 1999; Neves, Cooke, & Bliss, 2008; Wang & Morris, 2010). Complementarily, in the past few years considerable experimental attention has been paid to the study of the functional events taking place at the neuronal or synaptic levels during actual learning in alert behaving animals. Although obvious experimental limitations have been an important drawback to our understanding of functional neural states supporting the acquisition of new adaptive abilities (Delgado-García & Gruart, 2002), recent technical developments are increasingly allowing the study, at multiple cortical and subcortical synaptic sites, of learning phenomena at the very moment of their acquisition, extinction, or retrieval (Carretero-Guillén, Pacheco-Calderón, Delgado-García, & Gruart, in press; Gruart, Sánchez-Campusano, Fernández-Guizán, &

Abbreviations: EMG, electromyographic; fEPSP, field excitatory post-synaptic potentials; HFS, high-frequency stimulation; LTP, long-term potentiation; mPFC, medial prefrontal cortex; NMDA, *N*-methyl-D-aspartate; PP, perforant pathway; SUB, subiculum; REU, reuniens; NAc, nucleus accumbens septi; CS, conditioned stimulus; US, unconditioned stimulus.

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Delgado-García, in press). In addition, the use of optogenetic tools has greatly enlarged the types of experimental approaches than can be carried out in behaving animals during learning tasks (Ramirez, Liu, Lin, Suh, Pignatelli, Redondo, Ryan, & Tonegawa, 2013; Redondo, Kim, Arons, Ramirez, Liu, & Tonegawa, 2014; Shipton, El-Gaby, Apergis-Schoute, Deisseroth, Bannerman, Paulsen, & Kohl, 2014).

At the same time, it is also generally assumed that LTP is the most feasible mechanism underlying associative learning (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973; Cooke & Bear, 2012; McNaughton, Douglas, & Goddard, 1978). LTP is usually evoked (both in vitro and in vivo) by high-frequency stimulation (HFS) of selected afferent pathways, resulting in a long-lasting enhancement of synaptic efficacy. It is also generally accepted that, in most cases, the necessary and sufficient condition for evoking LTP is the activation of NMDA receptors (Bliss & Collingridge, 1993; Collingridge, Kehl, & McLennan, 1983a, 1983b; Harris, Ganong, & Cotman, 1984; Malenka & Nicoll, 1999). Thus, it can be assumed that the experimental blockage of NMDA receptors in behaving animals should be able to prevent LTP, as well as the acquisition of associative learning and the concomitant changes in synaptic strength (Hebb, 1949; Konorski, 1948).

Here we will present a series of experimental studies carried out in our laboratory during the past ten years considering the relationships between experimentally evoked LTP, changes in synaptic strength evoked by actual learning, and the role of NMDA and of many other receptors, mediators, and transcription factors involved in learning and memory processes (Gruart, Muñoz, & Delgado-Garcia, 2006; Madroñal, Delgado-García, & Gruart, 2007). Particular attention will be paid to the contribution of specific hippocampal, prefrontal, and other cortical and subcortical circuits to the acquisition to the two main types of associative learning, represented by the classical conditioning of eyelid responses, and selective operant conditioning tasks (Carretero-Guillén et al., in press; Eleore, López-Ramos, Yi, & Delgado-García, 2007; Gruart et al., in press; Jurado-Parras, Sánchez-Campusano, Castellanos, del-Pozo, Gruart, Delgado-García, 2013; Leal-Campanario, Delgado-García, & Gruart, 2013).

2. The hippocampal CA3–CA1 synapse is modified during the acquisition of new motor and cognitive abilities

In accordance with the above contentions, we will firstly consider here changes in synaptic strength taking place in a well-known synapse of the intrinsic hippocampal circuit (i.e., the synapse between Schaffer collaterals and the apical dendrites of the CA1 area). In an initial study, Gruart et al. (2006) attempted to determine whether the acquisition of a particular type of associative learning modifies the synaptic strength of the hippocampal CA3–CA1 synapse during the actual learning process. For the associative learning task, we used the classical conditioning of eyelid responses, with a trace paradigm (Fig. 1A, B), a training process involving the hippocampal circuit (Berger, Rinaldi, Weisz, & Thompson, 1983; McEchron & Disterhoft, 1997; McEchron, Tseng, & Disterhoft, 2003; Moyer, Deyo, & Disterhoft, 1990; Múnera, Gruart, Muñoz, Fernández-Mas, & Delgado-García, 2001; Thompson, 1988). Wild-type mice were presented with a short-lasting (20 ms) tone as a conditioned stimulus (CS), followed, 500 ms from its start, by an electrical shock delivered to the trigeminal nerve as an unconditioned stimulus (US). Eyelid responses were determined by the electromyographic (EMG) activity of the orbicularis oculi muscle ipsilateral to US presentation. To record the synaptic events taking place at the hippocampal CA3–CA1 synapse during the acquisition process, Gruart et al. (2006) recorded in vivo field excitatory post-synaptic potentials (fEPSPs) evoked at the apical dendrites (stratum radiatum) of hippocampal CA1 pyramidal cells (contralateral to US presentation) by the electrical stimulation of the ipsilateral Schaffer collateral-commissural pathway. fEPSPs were evoked during CS–US intervals (300 ms after CS presentation) across three different learning situations: habituation, conditioning, and extinction. As illustrated in Fig. 1C, the slope of fEPSPs evoked 300 ms after CS presentations increased steadily during conditioning and decreased during extinction sessions, presenting no significant changes during the four habituation sessions. fEPSP slopes increased during conditioning and decreased during extinction proportionally to the percentage of conditioned responses evoked during these two experimental situations (Fig. 1C, D). Thus, it was concluded from this early study that the CA3–CA1 synapse underwent a slow modulation (i.e., potentiation, or decrease) in synaptic strength (Bliss & Collingridge, 1993; Hebb, 1949; Kandel, 2001) across the different conditioning situations in parallel with the acquisition and/or extinction of conditioned eyelid responses. In a seminal study, Weisz, Clark, and Thompson (1984) had already reported a similar change in efficacy at the PP–DG synapse during nictitating membrane response conditioning in behaving rabbits.

Apart from the description made here regarding the involvement of the hippocampal intrinsic circuit in the acquisition of the particular type of associative learning represented by the classical eyeblink conditioning (Berger et al., 1983; Gruart et al., 2006; McEchron & Disterhoft, 1997; Moyer et al., 1990), the hippocampus seems to participate in other different functions, such as spatial orientation (Moser, Kropff, & Moser, 2008), object recognition (Clarke, Cammarota, Gruart, Izquierdo, & Delgado-García, 2010), and other forms of memory acquisition, storage, and retrieval (Bliss & Collingridge, 1993; Neves et al., 2008; Wang & Morris, 2010). In contrast, it has been recently shown that the hippocampus is not very much involved in the entire process of the acquisition of instrumental learning tasks (Jurado-Parras, Gruart, & Delgado-García, 2012; Jurado-Parras et al., 2013), although the CA3–CA1 is modulated in strength by the performance of specific appetitive (e.g., pressing a lever in order to obtain a piece of food) vs. consummatory (e.g., eating the collected pellet) behaviors (Jurado-Parras et al., 2013). This involvement of the hippocampus in specific behaviors related to operant conditioning tasks is extensible to appetitive reinforcements (pressing a lever to obtain an electrical stimulation of a positive reinforcing center, such as the medial septum) vs. internal ones (in order to receive the self-stimulation) (Vega-Flores, Rubio, Jurado-Parras, Gómez-Climent, Hampe, Manto, Soriano, Pascual, Gruart, & Delgado-García, 2014).

3. Acquisition of hippocampal-dependent classically conditioned eyelid responses is prevented by experimentally evoked LTP at the CA3–CA1 synapse

The following question was addressed in the Gruart et al. (2006) study: does experimentally evoked LTP share some synaptic mechanisms with learning-dependent changes in synaptic functioning? By that time, it had already been reported that place representation in hippocampal networks can be modified by experimentally evoked LTP (Dragoi, Harris, & Buzsáki, 2003), and that LTP saturation of hippocampal circuits disrupts spatial learning (Barnes, Jung, McNaughton, Korol, Andreasson, & Worley, 1994). Furthermore, hippocampal CA1 kindling has similar disrupting effects on spatial memory performance in behaving rats (Stan Leung & Shen, 2006). In accordance, it could be confidently predicted that the experimental induction of LTP in selected synapses of the intrinsic hippocampal circuit would be capable of disturbing the physiological synaptic changes taking place at the different stages of the classical conditioning of eyelid responses.

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