Archives Italiennes de Biologie, 143: 143-156, 2005.

SYNAPTIC PLASTICITY AT THE CEREBELLUM INPUT STAGE: MECHANISMS AND FUNCTIONAL IMPLICATIONS

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INTRODUCTION

Long-term synaptic plasticity is a well-established biological process consisting in persistent changes in synaptic strength, which follow specific activity patterns in synapses and neurons (Bliss and Collingridge, 1993; Hawkins *et al.*, 1993; Malenka and Nicoll, 1999). Long-term synaptic plasticity is considered the cellular basis for learning and memory (Bliss and Collingridge, 1993; Bliss, Collingridge and Morris, 2003) and typically takes the form of potentiation, LTP, or depression, LTD. In fact, LTD is probably a separated process from depotentiation, the reverse of LTP (Lisman, 2003). LTP and LTD have been reported at several central synapses in the neocortex, hippocampus, cerebellum and other brain structures. Despite an amazing complexity and variety of mechanisms, LTP and LTD respect some general features which are reviewed below. Then, I'll consider the case of LTP at the mossy fiber – granule cell synapse of cerebellum, which is opening interesting perspectives on the relationship between synatpic structure, function and plasticity. The analysis of this new form of plasticity, together with others recently discovered in the cerebellum (Hansel *et al.*, 2001), provides new cues to explain cerebellar information processing and sensori-motor control.

GENERAL PROPERTIES OF LONG-TERM SYNAPTIC PLASTICITY

The existence of long-term synaptic plasticity was predicted by the theoretical work of Donald Hebb in 1947. Then, LTP was first demonstrated in the rabbit hippocampus *in vivo* by Bliss and Lomo in 1973. A parallel story developed in the cerebellum, where LTD at the parallel fiber – Purkinje cell synapse was predicted by David Marr in 1969 and subsequently demonstrated by Ito in 1982. These forms of LTP and LTD represent to date the most intensely investigated paradigms of synaptic learning in the mammalian brain.

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vation and activation of other second messenger systems involved in LTP/LTD can occur through activation of mGlu receptors.

Downstream of Ca^{2+}, several Ca^{2+} - sensitive enzymes (like CaMK-II, PKA, PKC, NOS) start the expression phase. CaMK-II plays a central role at least in hippocampal LTP, and has been proposed as a key element for channel phosphorilation and insertion in the postsynaptic membrane (Lisman, 1993). NOS is supposed to be the key element for trans-synaptic expression mechanisms. A noticeable example is LTD at the parallel fiber – Purkinje cell synapse of cerebellum, where NO (the gaseous diffusible neurotransmitter produced by NOS) released from granule cells determines postsynaptic changes. In the hippocampus, NO released from postsynaptic neurons could explain presynaptic increase in neurotransmitter release (Arancio *et al.*, 1996), although the issue is debated.

Several expression mechanisms have been reported and proved to vary from synapse to synapse and even during different stages of LTP. Two main categories of expression mechanisms can be recognized, the pre- and postsynaptic. In the presynaptic hypothesis, vesicular release is increased. This could occur through the action of a retrograde messenger (e.g. NO, see below) either because the number of releasing sites or their probability of release is increased. It should be noted that a site with zero release probability is presynaptically silent. In the postsynaptic hypothesis, synaptic channels can be modulated by phosphorilation or inserted into the synapse. Insertion may occur in discrete quantal units uncovering a postsynaptically silent site. Clearly, the potential existence of pre- or postsynaptically silent sites confuses quantal analysis (e.g. see discussion in Lisman, 2003; Kullman *et al.*, 1996), as considered below.

After an initial phase of about 30-60 minutes, synaptic strength is determined by new protein synthesis and gene expression probably affecting both the pre- and postsynaptic terminals. An important related issue is that of tagging (reviewed in Martin and Kosik, 2002; Sajikumar and Frey, 2004), so that protein trafficking can be properly directed and proteins addressed to the synapses which need to express LTP or LTD.

Non-synaptic mechanisms

In their original discovery of LTP, Bliss and Lømo (1973) reported the existence of E-S potentiation, a process increasing EPSP-spike coupling without intervention of a synaptic modification. Recently, the existence of non-synaptic plasticity has been documented in an increasing number of neurons, which change their intrinsic excitability in response to specific stimulus patterns (Zhang and Linden, 2003; Daoudal and Debanne, 2004). This form of plasticity is intrinsically different from classical neuromodulation (e.g. by acethylcholine of noradrenaline) since it persists after the presentation of the stimulus and occurs at glutamatergic synapses. An important form of plasticity that could be confused with E-S potentiation is that occurring at inhibitory synapses. Since these eventually control GABA-A receptors and cell input resistance, they will eventually regulate neuronal intrinsic excitability.

vered by Ito (Ito *et al.*, 1982). However, most influential cerebellar theories neglect the existence of plasticity at the mf-GrC relay. For instance, Marr (1969) explicitly negated the possibility that mf-GrC synaptic weights could be modified by activity. He noted that "*sooner or later all weights would be saturated*" so that plasticity would be inefficient. Thus, the Marr's model did not include any mf-GrC synaptic plasticity, although the subsequent extension due to Albus (1971) was more permissive. However, the observation that mfs discharge consists of high-frequency bursts (Kase *et al.*, 1984; Chadderton *et al.*, 2004)) and that GrCs express NMDA receptors, which trigger the induction of LTP/LTD at other central synapses (see Bliss and Collingridge, 1993; Hawkins *et al.*, 1993; Malenka and Nicoll, 1999), led us to revisit the question. In fact, once theta-burst stimulation or prolonged (1 sec) high-frequency (100 Hz) stimuli were applied to mfs in cerebellar slices, GrC synaptic exci-

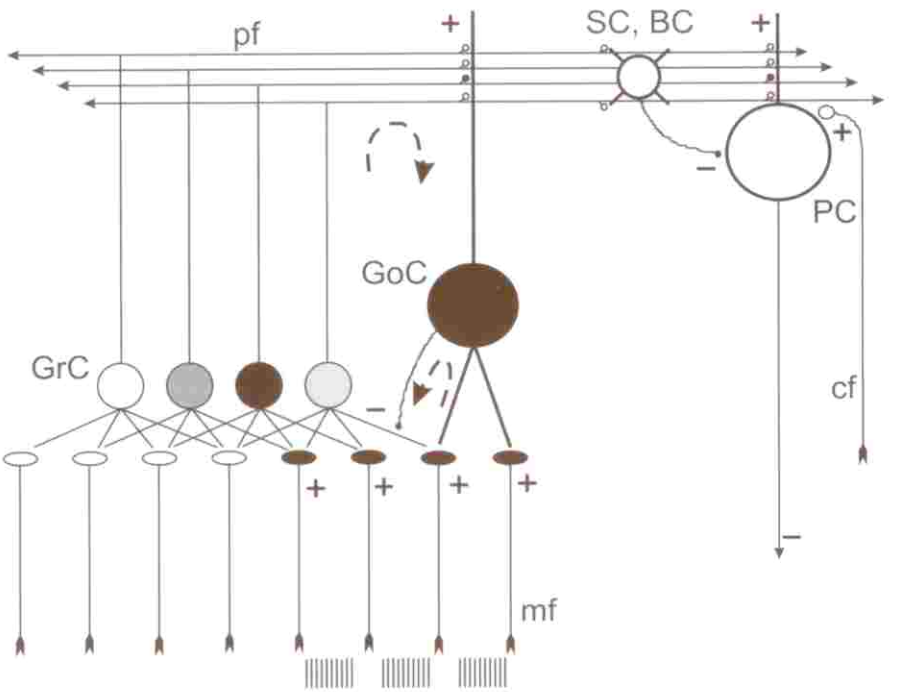

Fig. 1. - *Schematic representation of the neuronal circuit of the cerebellar cortex: mf, mossy fiber; pf, parallel fiber; cf, climbing fiber; GrC, granule cell; GoC, Golgi cell; PC, Purkinje cell; SC, stellate cell; BC, basket cell.*
The granular layer is primarily composed of GrCs and GoCs. Note divergence and convergence at the mf-GrC relay and the double feed-back and feed-forward inhibition of GrC through GoC (dashed arrows). SC, BC, PC are outside the granular layer. Inhibitory neurons are in black and arrows indicate the direction of information flow. Excitation of mossy fibers with bursts of action potential (e.g. a theta-burst stimulation, TBS, consisting of 100-Hz 100-ms bursts repeated every 250 ms) actives a certain set of granule cells, some of which are inhibited by Golgi cells. The cell depicted in red is strongly excited by 2 mfs, the one in yellow is weakly excited by 1 mf, the one in blue (although also receiving mf excitation) is inhibited by the Golgi cell. According to our investigations (Armano *et al.*, 2000) the cell in red will generate LTP and the one in yellow will generate potentiation of intrinsic excitability, while the one in blue could generate LTD.

(D'Angelo *et al.*, 1999; Fig. 3A). A presynaptic mechanism of expression during the first 30 minutes of LTP has been supported by a recent investigation (Sola *et al.*, 2004). The demonstration is based on several points. First, during LTP, EPSC coefficient of variation (CV), failures and paired-pulse ratio (PPR) decreased. Similar changes were observed by raising neurotransmitter release (high Ca^{2+}/Mg^{2+}), while the opposite occurred by decreasing release (low Ca^{2+}/Mg^{2+}, Cl-adenosine). No changes followed postsynaptic modifications (different holding potential), while only CV and failures decreased by raising the number of active synapses. LTP was occluded by raising release probability and was observed in the spillover-dependent component of AMPA EPSCs and in NMDA EPSCs. Finally, during LTP, minis did not change their amplitude or variability but increased their frequency. Binomial analysis explained EPSC changes through an increased release probability. It should be noted that these observations may not be sufficient due to the several complications depending on synaptic organization. However, we recall that neither AMPA nor NMDA receptors are saturated at this synapse allowing quantal analysis to be applied in its classical terms. Moreover, spillover increased both the AMPA and NMDA EPSC, as expected from increased release in the glomerulus. Finally, short-term plasticity changes during LTP are consistent with a presynaptic modification (Nieus, Sola, Mapelli, Saftenku, Rossi and D'Angelo, submitted). Thus, mf-GrC LTP makes a particularly well documented case of presynaptic LTP expression.

As well as in mf-GrC LTP, an increased neurotransmitter release was proposed to occur at other central synapses *in situ* (Malinow and Tsien, 1990; Schultz *et al.*, 1994; Kullmann *et al.*, 1996; Gasparini *et al.*, 2000) and in neuronal cell cultures (Bekkers and Stevens, 1990; Malgaroli *et al.*, 1995). Coupling between postsynaptic NMDA receptor-dependent induction and presynaptic expression may be provided by NO (Arancio *et al.*, 1996). Indeed, blocking NOS, scavenging NO, or blocking sGC prevented mf-GrC LTP, while NO donors induced it (Maffei *et al.*, 2003). The present observation does not exclude that, in different functional or developmental conditions, LTP expression might change. For instance, silent synapse awakening characterizes the developmental process of the cerebellar mf-GrC relay, leading from purely NMDA to mixed AMPA-NMDA EPSCs (see above: D'Angelo et al. 1993; Losi *et al.*, 2002). Moreover, NMDA receptor stimulation leads to CREB activation in GrCs (Monti *et al.*, 2002), and may therefore prime postsynaptic gene expression and protein synthesis in later LTP phases.

Mf-GrC LTP expression: changes in GrC intrinsic excitability

In addition to showing an increased synaptic conductance, during LTP GrCs show an increased intrinsic excitability (Armano *et al.*, 2000; Fig. 3A). GrC E-S potentiation can be identified in the presence of blockers of inhibitory transmission and reflects therefore changes in intrinsic excitability. GrC E-S potentiation consists of an increased input resistance in the subthreshold region and of a spike threshold decrease. E-S potentiation is induced by NMDA receptor activation but is less sensitive to membrane depolarization than potentiation of synaptic conductance. Thus, a protracted weak stimulation may be able to enhance GrC excitability, and E-S potentiation would assume an homeostatic effect. Clearly, E-S potentiation is all

As every feed-forward device, the cerebellum needs to store information to be used in a predictive manner. No surprise therefore that the cerebellar circuitry expresses mechanisms for learning and memory. As proposed by Marr (1969), a major form of plasticity occurs at the pf-PC synapse, allowing eterosynaptic depression when a motor error is detected (pf-PC LTD). Instruction or error signals are conveyed by cfs, so that pf-PC synapses relaying relevant sensori-motor signals are persistently depressed. The experimental observation of pf-PC LTD has obviously a huge impact on present understanding of cerebellar functions (reviewed by Ito, 2001). Nonetheless, the discovery of mf-GrC LTP, together with various forms of plasticity at other cerebellar synapses, suggests that the classical concept of cerebellar learning needs to be extended (Hansel *et al.*, 2001; see also Llinas *et al.*, 1997; DeSchutter 1997).

By being induced by omosynaptic activity, mf-GrC LTP implements a modality of unsupervised learning. By being dependent on high-frequency mf activity and postsynaptic depolarization, LTP is associative, implementing a process of coincidence detection. The functional consequences of mf-GrC LTP depend on several factors including the molecular and cellular mechanisms involved, the spatial distribution of plasticity, local network activity (primarily related to endogenous rhythms and synaptic inhibition), and long-range modulation (primarily related to cholinergic, serotoninergic and noradrenergic innervation of the cerebellum). Although understanding of these mechanisms is far from being complete, some hypothesis can be advanced.

1) The enhanced release probability during LTP is associated with complex changes in short-term neurotransmission dynamics. During LTP, short-term synaptic depression is enhanced and the spillover current is increased. This remarkably anticipates the first-spike latency and raises the frequency of output bursts (Nieus, Sola, Mapelli, Rossi and D'Angelo, *in preparation*). Thus, mf-GrC LTP may play an important role in regulating temporal recoding in the cerebellum (DeSchutter and Bjiale, 2001) providing the substrate for adaptable delay lines envisioned by theoretical models of the cerebellum (Braitenberg, 1967; Medina and Mauk, 2000).

2) Since EPSC variability decreased (Sola *et al.*, 2004), LTP should improve the reliability of neurotransmission. The effect could be an increase in mutual information transfer (MI), a subject currently under investigation (Bezzi, Nieus, Coenen, and D'angelo, unpublished observations). Optimization of MI is indeed at the core of two recent theories on granular layer function. In the first (Schweighofer *et al.*, 2000), LTP enhances MI while the postsynaptic increase in intrinsic excitability (Armano *et al.*, 2000) is suited for determining the number of active GrCs minimizing redundancy and optimizing sparse representation of mf activity. In the second (Philippona and Coenen, 2003), LTP follows to an unsupervised learning rule intrinsic in the glomerular structure requiring a global feedback signal that could correspond to NO.

3) A critical step in understanding LTP functional implications is that of defining the *learning rules* (Siöström and Nelson, 2002). What we know is that a single 100-

APPENDIX

Synaptic transmission at the mf-GrC relay

Mossy fibers (mfs) form the largest cerebellar afferent system and originate from various regions in the spinal cord, brain-stem, and cerebral cortex. Mfs activate GrCs and Golgi cells (GoCs), the main inhibitory interneurons of the granular layer. Golgi cells are also excited by parallel fibers (pf), the GrC axons. Thus, GoCs inhibit GrCs through a double feed-forward and feed-back loop. The excitatory nature of the mf-GrC synapse and its inhibitory control by Golgi cells were early recognized (Eccles *et al.*, 1967). Mfs diverge onto numerous GrCs (about 28 in the rat), which in turn receive just 4 different mf inputs on as many independent dendrites. GrCs dendrites terminate with 3-4 bulbs endowed with postsynaptic densities aligned with releasing sites in the mf terminal (Hamory and Somogy, 1983; Jakab and Hamory, 1988). Miniature synaptic currents are uniquantal (Chatala *et al.*, 2003) and quantal analysis indicates that EPSCs are determined by release of 1 to 3 quanta (Sola *et al.*, 2004), as expected from ultrastructural investigation. The probability of release estimated with binomial models ranges from 0.2 to 0.7. Mf are glutamatergic and activate AMPA, NMDA, and mGlu receptors in GrCs. AMPA receptors are located in clusters facing the releasing sites (DiGregorio *et al.*, 2003), while NMDA receptors are in part synaptic and in part extrasynaptic (Rossi *et al.*, 2002; Petralia *et al.*, 2002; Chatala *et al.*, 2003). Glutamate spillover in the glomerulus can activate both AMPA receptors located at different postsynaptic sites and NMDA receptors. Non-stationary fluctuation analysis (Silver *et al.*, 1996) and analysis of the spillover current (DiGregorio *et al.*, 2003; Sola *et al.*, 2004) indicate that neither AMPA nor NMDA receptors are saturated by synaptically released glutamate. Spillover is also thought to generate a remarkable AMPA receptor desensitization contributing to shape EPSC dynamics during repetitive neurotransmission (Xu-Friedmann and Regher, 2003). EPSPs generated by a single mf are usually not sufficient to activate an action potential from rest, and the synchronous activation of 2-3 synapses is needed (D'Angelo *et al.*, 1995). During repetitive stimulation, the ongoing depression in AMPA receptor-mediated responses is compensated by a large increase in spillover currents (AMPA and NMDA) enhancing temporal summation. Glutamate also activates class-I mGlu receptors coupled to the PIP_2 pathway. Both NMDA and mGlu receptors play an important role in regulating GrC intracellular Ca^{2+} increase (Gall *et al.*, 2004; Gall, Prestori, Sola, Rossi and D'Angelo, unpublished observation).

Acknowledgments. - Supported by European Community grants IST-2001-35271 and QLG3-CT-2001-02256, by MIUR and INFM of Italy.

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