REVIEW

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The Cerebellum, LTD, and Memory: Alternative Views

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Introduction

The idea that cerebellum stores motor memories has become so commonplace in the scientific literature that it is often presented uncritically as a fact. Even many of today's medical school textbooks state that motor memories are localized in the cerebellum and that the subcellular substrates of these memories have been identified in that structure. Such prospects, if true, would be very exciting; however, it should be pointed out that there is nothing close to unanimity among cerebellar scientists on even the most basic of these points and that any consensus about "cerebellar motor learning" represents the view of a limited number of research groups that perform experiments on a limited number of preparations. Thus, one point of our paper is to emphasize that the idea of cerebellar motor learning has not been demonstrated and thus remains one of the most highly speculative hypotheses in the neurosciences—even after more than three decades of active investigation. A second issue is that rules for the alleged cellular substrate of motor learning, long-term depression (LTD) of Purkinje cell activity, have become so indeterminate and ambiguous as to justify a total reevaluation of the idea that LTD is a bona fide mechanism of any learning process. That point is significantly reinforced by a critical evaluation of the most recent behavioral and neurophysiological data obtained from gene knockout rodents. Nevertheless, an impressive volume of research has been performed on the cerebellar systems in the context of cellular-molecular biology and behavior. Thus, we may now place many of those findings into a modern context to formulate hypotheses that are more easily testable than the rather timeworn idea of "cerebellar learning."

As is well recognized, the concept of "cerebellar motor learning" originates from the highly speculative and completely theoretical works of Brindley (1964), Marr (1969), and Albus (1971). These works can be credited for their clarity and breathtaking views of the cerebellar neuronal circuitry. These works were so bold as to specify distinct functions for each of the inhibitory interneurons of the cerebellar cortex—Golgi, basket, and stellate cells—during the learning process, neurons about which very little *in vivo* neurophysiology has ever been obtained, even with our advantage of 30 years of further research. Nevertheless, the most critical aspect of the Brindley-Marr-Albus models was the assumption that the climbing fibers had to play a "teacher" role for the purpose of modifying the efficacy of the parallel fiber-Purkinje cell synapse. The functional consequence of such climbing fiber-induced plasticity was to change the pattern of Purkinje cell output in specific sensory contexts to generate novel (i.e., learned) movements. In these conceptions, the olivocerebellar system played only an indirect role in movement, through its functional interaction with parallel fiber synapses. Conversely, the mossy fiber-parallel fiber system was viewed as a motor command system

that elicited movements of a particular form depending on the excitability state of the Purkinje cell population and the pattern of mossy fiber input at any given time. This is the view on which all advocates of “cerebellar motor learning” rely.

The reason why the Brindley-Marr-Albus hypotheses of cerebellar function have been so captivating has had as much to do with the absence of as unifying a view as with the clarity of their presentation (see Llinás and Welsh 1993). Simply put, if the Brindley-Marr-Albus hypotheses were true, even in broad outline, they would succinctly explain the entire cerebellum with one broad stroke. Hope for the unifying hypotheses was stimulated when LTD of the parallel fiber-Purkinje cell synapse was found following the pairing of parallel fiber and climbing fiber stimulation (Ito et al. 1982), and the momentum from that discovery has carried us to the present day.

LTD: What Are the Rules and How Do They Apply?

Until recently, nearly all demonstrations of Purkinje cell LTD have used coincident stimulation of climbing fibers and parallel fibers. A parametric study of the timing relationships necessary for LTD showed that sequenced stimulation of climbing fibers and parallel fibers would also result in LTD but that climbing fiber stimulation had to precede parallel fiber stimulation to generate LTD (Karachot et al. 1994). Presciently, both Marr and Albus had stated that the only parallel fiber input that could be modified in cerebellar learning was that which occurred immediately after climbing fiber input, and the *in vitro* studies reinforced that view.

The situation has changed considerably in the last 2 years. First, it has been demonstrated that LTD does not require climbing fibers: Parallel fiber input alone can produce an LTD just as robust, if not more, than climbing fiber-parallel fiber LTD (Hartell 1996). Second, others have found that the ordering of climbing fiber-parallel fiber LTD is not critical: Parallel fiber stimulation 100–200 msec prior to climbing fiber stimulation can produce LTD (Chen and Thompson 1995). So, now LTD is recognized as a cellular phenomenon that can occur under a wide variety of conditions, seemingly without specificity for either the ordering of the stimulated afferents or the stimuli themselves. Thus, LTD as a cellular phenomenon is much more nonspecific and general than was ever envisioned in the context of learning. This raises concerns for whether LTD can underlie the unique types of learning that are commonly studied in this regard, namely, classical conditioning of eye-blink reflexes and gain modification of the vestibulo-ocular reflex, because the stimulus conditions under which they occur are very highly specific (Coleman and Gormezano 1971; du Lac et al. 1995).

LTD: The Signal-to-Noise Problem

LTD as a mechanism for learning-related synaptic plasticity in the cerebellum has long been recognized as being incomplete, because, for example, if it were unopposed, suppression of all parallel fiber synapses would result from ongoing spontaneous activity. This problem has been raised by Albus (1971) and others (du Lac et al. 1995), and solutions have included either a slow decay of the LTD back to baseline or a complementary excitatory mechanism such as LTP. Although such proposals would eliminate the suppression problem, they do not explain the extraordinary persistence that motor memories may have in the absence of performance of the specific act. In particular, they do not

address the signal-to-noise problem that arises with any spontaneously active system and that is particularly acute for Purkinje cells, given spontaneous granule cell firing rates on the order of 10–50 Hz (Eccles et al. 1966). In the presence of such spontaneous rates of parallel fiber input, there is a 0.1–0.5 probability that a particular parallel fiber synapse will be active during a complex spike (CS) triggered by a climbing fiber (assuming only a 10-msec duration for the CS). This implies that in 10 sec (assuming a CS firing rate of 1 Hz and parallel fiber firing rate of 50 Hz), >99.9% of the parallel fiber–Purkinje cell synapses would be modified at least once. This is hard to reconcile with the permanence of motor memories.

To rescue the Marr–Albus hypotheses from the above problem, some investigators have postulated an essential role for a climbing fiber-triggered plateau potential (Ekerot and Oscarsson 1981). Although it is not clear that such plateau potentials are necessary for LTD (Sakurai 1987), its attenuation by inhibitory input to Purkinje cells provides a possible mechanism for distinguishing spontaneous from learning-related conjunctions (Ekerot and Kano 1985). There is support for this idea, because inhibitory inputs to the Purkinje cell may prevent LTD. Although this proposal may rescue the Marr–Albus hypotheses from the signal-to-noise problem, it paradoxically transfers the “teaching” role to the granule cells. This is because the inhibitory interneurons that innervate the Purkinje cells (stellate and basket) receive the vast majority of their input from granule cells. Thus, the pattern of granule cell firing would determine not simply which parallel fibers are active but which parallel fiber synapses are modified by the climbing fiber. Thus, to counter the signal-to-noise problem, the basic tenets of Brindley–Marr–Albus are violated.

Gene Knockouts of LTD: Weakening the Link

Recent investigations using gene knockout techniques have also weakened the link between the LTD and its proposed role in learning. One study using mGluR4 knockout mice showed that performance on a rotating-rod test of motor learning was impaired in the absence of any deficit in cerebellar LTD or in general performance (Pekhletski et al. 1996). Mice whose mGluR1 receptors are deleted (Aiba et al. 1994) do not have appreciable LTD but show an ability to improve their time on a stationary rotorod, despite a lower overall level of motor function. When more difficult tests were used, such as the rotating or inclined rotorods, these mice showed no motor learning. However, given their overall low level of performance, evidenced in the stationary rotorod and by their ataxia, it is impossible to interpret such acquisition deficits on the more difficult tasks (Harvey and Welsh 1996). Yet, in the same study, mGluR1 knockout mice showed normal classical conditioning of the eyeblink reflex for the first two sessions of conditioning and a normal rate of extinction after five sessions of conditioning. Although classical conditioning was intact in LTD and mGluR1 deficient mice, the asymptotic amplitude of the conditioned response was reduced by 30%. Thus, the data taken from mGluR1 knockout mice indicate that neither motor learning nor classical conditioning requires cerebellar LTD. In fact, the 30% decrease in the amplitude of the conditioned eyeblink response in mGluR1 deficient mice was precisely that estimated to be the cerebellar contribution to the longer-latency component of the conditioned response as determined by kinematic analysis (Welsh 1992).

In an interesting study, knockout of the γ isoform of PKC potentiated classical conditioning of the eyeblink reflex in mice but had no effect on the induction of LTD in vitro (Chen et al. 1995). Such mice showed a more rapid acquisition of conditioned eyeblink responses as compared with controls and were resistant to extinction—convincing data to show the strength of associations and their rate of formation is dissociable from the magnitude of LTD.

Finally, in a most recent study of mice deficient in GFAP, cerebellar LTD was impaired both in duration and amplitude (Shibuki et al. 1996). Purkinje cells from GFAP deficient mice show LTD for only 10 min after coincident climbing fiber–parallel fiber stimulation. Nevertheless, these mutant mice show a significant acquisition of eyeblink conditioning and clear day-to-day retention of memory, in contrast with the very brief duration of their LTD. Like the mGluR1 mutants, GFAP mutants showed an equivalent rate of extinction after eight sessions of conditioning, again reinforcing the conclusion that learning occurred in the absence of the capability for truly “L”-TD.

An Alternative Hypothesis: LTD as Damage Control

We would like to present a novel idea regarding LTD, namely, that it serves a neuroprotective function. A fact of LTD is that it is a response to excessive excitation of the Purkinje cell. It must be recognized that the Purkinje cell constantly is at risk for Ca-mediated excitotoxicity, because both of its major afferents (climbing fibers and parallel fibers) trigger Ca influx in its dendrites. Climbing fibers trigger powerful Ca spikes (Llinás and Sugimori 1980a,b) throughout the entire dendritic tree (Miyakawa et al. 1992), and recent studies with confocal microscopy (Eilers et al. 1995) and two-photon excitation imaging (Denk et al. 1995) have shown that parallel fiber input activates Ca channels, but more focally on dendritic spines. Quantitatively, the Purkinje cell receives up to 200,000 parallel fibers and a single climbing fiber that forms ~300 synapses (Llinás et al. 1969). It has been shown that glutamate induces a rise in intracellular Ca concentration in Purkinje cells (Llano et al. 1991; Sugimori and Llinás 1990, and unpubl.) and that Ca influx in Purkinje cells is linked to AMPA, glutamate, and kainic acid excitotoxicity (Brorson et al. 1994, 1995). Similarly, LTD appears to require increases in intracellular Ca concentration via the opening of voltage-gated Ca channels and the activation of AMPA and metabotropic glutamate receptors (Linden 1994).

In the face of massive excitatory inputs and, by comparison, limited inhibition to its dendritic tree, cerebellar LTD may serve as a significant damage control mechanism for the Purkinje cell. High intracellular Ca concentrations have been associated with cell death generally and Purkinje cell dendritic death in particular (Fig. 1; Llinás and Sugimori 1990). In accord with these findings, LTD might function to regulate the efficacy of individual synapses to prevent irreversible local lesions owing to excessive Ca influx from sustained synaptic bombardment. Recent experiments have demonstrated that secondary release of Ca from intracellular stores by IP₃ receptor activation can be activated by either afferent system, or direct iontophoretic application of glutamate to the dendritic arbor (M. Sugimori, B.D. Cherksey, and R. Llinás, unpubl.). This local damage can be blocked by heparin, a known IP₃ receptor blocker (M. Sugimori and R. Llinás, unpubl.). Such a role would be consistent with the original demonstration that LTD results from coincident parallel fiber–climbing fiber activation, the finding that noncontiguous climbing

Figure 1: Purkinje cell death is associated with a wave of high intracellular Ca concentration in the dendritic tree. Imaging of Ca-dependent Fura II fluorescent signals obtained from a Purkinje cell that ceased to generate action potentials and was characterized by a low input resistance (A). Determination of Ca concentration changes in the absence of extracellular Ca and of any type of electroresponsiveness are shown in B–F. (B) Localized increase in Ca concentration restricted to about the middle of the primary dendrite in the cell and to some of the dendritic branchlets arising from its immediate vicinity. This localized Ca concentration change then spreads slowly to the lower left dendritic branches localized immediately on top of the recording microelectrode (C). (D) Ca concentration increased upward to cover the dendritic tree to close to its upper bifurcation, whereas in E it moved decisively into the left portion of the dendritic arbor to its terminals, leaving most of the right branch of the dendritic tree intact. (F) The well-defined wave of intracellular Ca concentration covers all the dendritic tree. The process from B to F took ~20 min. The pictures were taken at equal intervals from B to F. The degree of Ca concentration change is represented by the degree of reduction in fluorescence, indicated here in pseudocolor, where red indicates a qualitative increase in $[Ca^{2+}]_i$. Taken from Llinás and Sugimori (1990).

fiber–parallel fiber stimulation produces LTD, and the most recent results showing that the precise ordering of climbing fiber and parallel fiber input is not critical for LTD and that parallel fiber stimulation alone can produce LTD. Finally, a damage control role for LTD is consistent with the minutes to hours time course of LTD decay, whereas such a time course represents a major difficulty for learning theories.

If Not LTD, Then What?

An alternative view of the olivocerebellar system is that it is directly involved in the ongoing modulation of movements. This view states that the olivocerebellar system (Fig. 2) generates coherent signals that serve to

Figure 2: The functional organization of the olivocerebellar system. The olivocerebellar system consists of three elements: Purkinje cells (PCs), cerebellar nuclei neurons (CNs, excitatory and inhibitory), and inferior olivary neurons (IOs, excitatory). IOs are electrotonically coupled (junctional contacts depicted by areas of overlap between short dendrites). Their axons project to the PCs as climbing fibers (green arrows) and to the CNs by axon collaterals. For simplicity, only one of these collaterals is shown. The PCs project to the CNs (black arrows). Climbing fiber activity fires PCs synchronously, generating powerful coherent inhibitory-postsynaptic potentials in the CNs. They follow the early excitation produced by the IO-axon-collateral systems. The inhibitory feedback implemented by the CN inhibition to the IO (yellow arrows at lower left) projects to the IO glomeruli, the site of IO electrotonic interaction. In this diagram, IO neurons being electrotonically coupled and intrinsically oscillating are viewed as pacemakers that forward their rhythmic activity to the cerebellum by climbing fibers and axon collaterals. Activation of the CN inhibitory feedback to IO is viewed as a superimposed pattern generator that regulates, dynamically, the degree of coupling between IO neurons and, in this manner, the number of pacemaker groupings that may be active at any particular time in the IO. CNs not projecting to the IO are excitatory and serve as pacemakers projecting to the forebrain, brain stem, and spinal cord. PCs are viewed as controlling the dynamic properties of the CN pattern generator. In this scheme, mossy fiber and climbing fiber afferents interact mainly at the CNs where maximum convergence of PC activity with afferent collateral activity takes place. Modified from Llinás and Welsh (1993).

bind in time the activation of the different muscle groups involved in making complex movement sequences (Llinás 1991; Welsh and Llinás 1997).

What is the evidence to support an independent role for the olivocerebellar system in motor function? First, the olivocerebellar system appears capable of generating motor output on its own. For example, pharmacological activation of the olivocerebellar system by harmaline (de Montigny and Lamarre 1973; Llinás and Volkind 1973) or by intraolivary injections of picrotoxin or tetraethyl ammonium (Lang 1995; Lang et al.

1996) results in sustained tremors that are driven by olivary activity. This occurs despite the fact that the average firing rate of CS activity remains relatively low during these manipulations (1–2.5 Hz; Lang et al. 1996). Furthermore, cooling of the cerebellar cortex does not prevent such tremorigenic activity (Llinás and Volkind 1973), indicating that olivocerebellar activity can generate movements independent of the parallel fibers and despite very low firing rates of individual olivary neurons.

If the average firing rate olivary activity is not critical for its ability to evoke movement, then what characteristic is important? One possibility is that the spatial distribution of synchronous firing within the olivocerebellar system is the critical parameter (Llinás 1991). Synchronization of spontaneous CS activity occurs most strongly among Purkinje cells located within 250- to 500- μ m-wide, rostrocaudally oriented strips of cortex (Fig. 3; Sasaki et al. 1989; Sugihara et al. 1993) and is dynamically controlled by the GABAergic cerebellar nucleoolivary pathway (Fig. 4; Lang et al. 1996). Evidence that synchronization of olivocerebellar activity is associated with the generation of vibrissal movements has been obtained electrophysiologically using motor cortex stimulation (Lang 1995; E.J. Lang, I. Sugihara, J.P. Welsh, and R. Llinás, unpubl.). In these experiments, a strong correlation ($r = 0.85$) was found between the probability of a motor cortex stimulus evoking a movement and the number of Purkinje cells in Crus IIa displaying synchronous CS activity. In particular, the critical parameter for whether a motor cortex stimulus would evoke a movement was the degree of synchronous firing within the olivocerebellar system immediately after the stimulus.

Results from a multiple electrode experiment involving conditioned tongue movements (Welsh et al. 1995a) or synergistic movements of the arm and tongue (J.P. Welsh, E.J. Lang, R. Marquez, and I. Sugihara, unpubl.) have provided direct evidence in awake animals that the patterns of synchronization of CS activity across the cerebellar cortex are related

Figure 3: (A) Diagram of multiple glass microelectrode placement for recording CSs from the cerebellar cortex. In this experiment, CSs from 40 Purkinje cells located on the surface and the rostral folial wall of Crus IIa were recorded. (B) The spatial distribution within the folium of CS synchrony with respect to cell M. The position of each electrode is represented by a circle. The area of each circle is proportional to the degree of simultaneous firing (i.e., within 1 msec) as determined by the calculation of a cross-correlation coefficient. Modified from Sugihara et al. (1993).

Figure 4: Change in the spatial pattern of CS synchrony by lesion of the dentate nucleus. Recordings were obtained from 42 Purkinje cells located on the surface of Crus IIa. (A) CS synchrony is organized in rostrocaudal bands in a control state. (B) After excitotoxic lesion of the dentate nucleus with NMDA, the medial–lateral extent of CS synchrony is increased. Interelectrode distance is 250 μ m. Data are presented as described in Fig. 3. Modified from Lang et al. (1996).

to movements. In experiments in which rats made conditioned protrusions of their tongue, it was found that only relatively small changes in CS firing rates occurred during movement, consistent with previous investigators, but that the patterns of synchronous CS activity changed significantly from the spontaneous patterns (Welsh et al. 1995). Taken together, the experiments on vibrissa, tongue, and arm movements suggest a strong relation between olivocerebellar synchrony and movement.

Conclusions

The proper execution of complex movement sequences requires the selection and appropriately timed activation of independent groups of motor neurons, where each group may generate a distinct elementary movement. A central role for the inferior olive in combining these independent groups to form complex movements is a hypothesis that emerges from multielectrode analysis of the olivocerebellar system. It has long been known that cerebellar or olivary damage leads to a decomposition of complex movements.

The most recent techniques have provided an entirely new perspective on cerebellar function. Whereas gene knockout experiments have weakened the link between cerebellar LTD and learning, multielectrode experiments have strengthened the link between climbing fiber activity and motor performance. It is clear that the operating principles of the

cerebellum will not be revealed in the one broad stroke that the Brindley–Marr–Albus hypotheses provided. Yet, the future holds much promise.

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