PROGRESS IN BRAIN RESEARCH
114: 529-542, (1997).

Editors: De Zeeuw C.I., Voogd J., Strata P.

A New Functional Role for Cerebellar Long Term Depression

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Introduction

Long-term depression (LTD) of excitatory synaptic transmission has been described in several regions of the brain (Artola and Singer, 1993; Linden, 1994). In most cases, the opposite process, i.e. long-term potentiation (LTP) (Bliss and Collingridge, 1993), is present at the same synapses. Most theories on the functional role of LTD in such neurons assume that LTD acts by resetting synapses that have undergone LTP (Tsumoto, 1993; Linden, 1994). In the cerebellum, however, LTD of the parallel fiber to Purkinje cell synapse (Ito, 1989) is distinguished by the absence of LTP at this synapse (Artola and Singer, 1993). This form of LTD has been extensively investigated in the context of a specific theory of the function of the cerebellum, first proposed by Marr (Marr, 1969) and subsequently elaborated by Albus (Albus, 1971) and Ito (Ito, 1984). However, the conditions under which cerebellar LTD can be induced *in vitro* do not seem to be compatible with some predictions of the Marr-Albus-Ito theories (Schreurs and Alkon, 1993). I will first review and criticize the Marr-Albus-Ito theories and then describe the properties of Purkinje cells and of LTD induction that are relevant to a new hypothesis on the function of cerebellar LTD that I have proposed recently (De Schutter, 1995a).

Synaptic circuitry of the cerebellar cortex

A remarkable property of the cerebellum is the uniformity of its cortical architecture (Ito, 1984). Purkinje cells receive two types of excitatory inputs: climbing fibers (CF) from the inferior olive and parallel fibers (PF) from cerebellar granule cells. Each Purkinje cell receives only one CF input, which evokes a powerful voltage-gated Ca^{2+} spike in the dendrite (Llinás and Sugimori, 1980; Knöpfel *et al*., 1991; Miyakawa *et al*., 1992), called the complex spike (CS). In contrast, 150,000 to 200,000 PF synapses (Harvey and Napper, 1991) contact each Purkinje cell, and generate conventional dendritic EPSPs.

Purkinje cells receive inhibition from basket cells and stellate cells. Both types of inhibitory neurons are excited by PF axons and therefore provide pure feedforward inhibition. Except for the sparse Purkinje axon collaterals (Bishop, 1982; Ito, 1984), there are no feedback connections between Purkinje cells and the rest of the cerebellar cortex. The feedforward excitation and inhibition in the molecular layer of the cerebellum is in sharp contrast with allo- and neocortex, where pyramidal cells receive massive feedback excitation and inhibition (Shepherd, 1990).

The Marr-Albus-Ito theories

Since Hebb (1949) first proposed that a synaptic modification based on the co-occurrence of pre- and postsynaptic activity might underlie learning, it has generally been assumed that synaptic plasticity plays a fundamental role in memory. An example is the theory of motor learning by the cerebellar cortex first proposed by Marr (1969) more than 25 years ago, which is an influential example of trying to deduce

neural function from structure. Marr proposed that PF synapses onto Purkinje cells are facilitated when they are activated together with the CF. In this theory the cerebellum learns motor skills by storing memory traces at the PF synapse under instruction of the olivary nucleus, which would signal correct performance. A few years later, Albus (1971) refined this theory by suggesting that the cerebellum functions as a modified perceptron (Minsky and Papert, 1969) pattern-classification device, with the complex spike as the unconditioned stimulus and mossy fiber (MF) input as the conditioned stimulus. Albus also proposed that the CF stimulus is an error signal and that the PF synapse is weakened instead of facilitated. This last hypothesis became known as the Marr-Albus theory (Fig. 1), which predicted the existence of LTD before any plasticity of synapses onto Purkinje cells was found. The theory was further extended by Ito in his flocculus hypothesis (Ito, 1984)

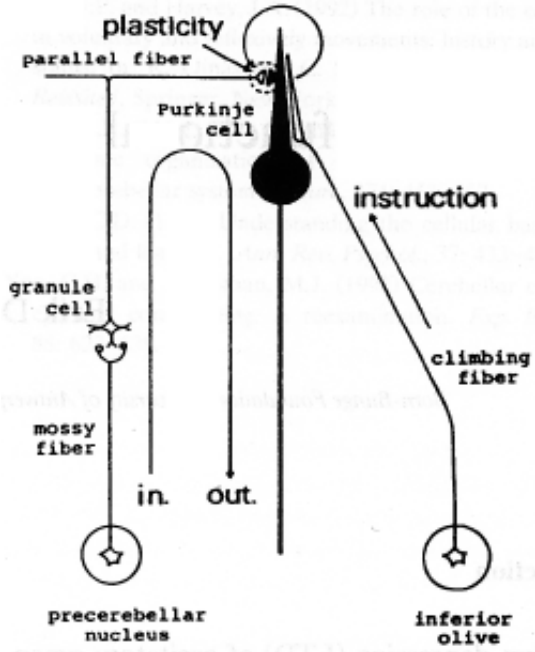

Fig. 1: Schematic illustration of the synaptic plasticity assumed in the Marr-Albus theory of motor learning in the cerebellum. Modified with permission from Ito (1984).

The Marr-Albus-Ito theories have always been controversial (Llinás, 1981; Thompson, 1986; Lisberger, 1988; Bloedel, 1992). In the early eighties, when the first experimental indications for the presence of LTD in Purkinje cells were found (Ito *et al*., 1982), discussions presented the mere existence of LTD as a proof of the Marr-Albus theory (Ito, 1989) and vice versa (Llinás and Yarom, 1981). Even now, most investigators of the mechanisms underlying LTD automatically assume that it plays a role in motor learning (Linden *et al*., 1991; Konnerth *et al*., 1992). More recent theories of motor learning involving the cerebellum also require LTD as the biophysical substrate of memory (Ito, 1989; Houk *et al*., 1990).

A critique of the Marr-Albus-Ito theories

This section presents a brief overview of the experimental work of the last decade which is relevant to the Marr-Albus-Ito theories. The goal of this overview is not to be complete, but to support the argument that it has not been proven experimentally that the cerebellar circuit is the neuronal substrate for motor learning and that some evidence actually suggests that cerebellar LTD is not an important factor in such learning. This does not imply that the cerebellum plays no role at all in motor learning, but that its function is more indirect than the Marr-Albus-Ito theories suggest.

The function of the cerebellum in motor learning has been extensively investigated in the context of classical conditioning of simple motor acts (Thompson, 1986; Lisberger and Pavelko, 1988; Hardiman and Yeo, 1992; Harvey et al., 1993; Krupa *et al*., 1993; Perrett *et al*., 1993). Unfortunately the literature on this subject is inconclusive, with many authors contradicting each other. This may be because most of the results are based on lesion studies, for which it is difficult to distinguish between performance deficits and

learning deficits (Bloedel, 1992) and because of variations in the location and extent of the lesions. As such this experimental approach has not provided convincing proof that the cerebellum is the site of motor learning.

A recent addition to this approach was the use of knockout mice to study the function of LTD. LTD is absent in mice (Aiba *et al*., 1994b; Conquet *et al*., 1994) lacking a metabotropic glutamate receptor subtype (Nakanishi, 1992). When such mutants are trained on the eye blink reflex using a standard paradigm of classical conditioning (Thompson, 1986), they can learn as well as normal animals during the first 3 days of training, but on the fourth and fifth day the mutant animals learn significantly less (Aiba *et al*., 1994b). As is often the case with knockout mice (Routtenberg, 1995), this result is difficult to interpret. However, it is impossible to reconcile the initially normal learning with the Marr-Albus-Ito theories. Moreover, it is difficult to attribute the learning deficits during the later phase to any specific brain location, because these animals also show reduced hippocampal LTP (Aiba *et al*., 1994a) and potential synaptic plasticity deficits in other brain structures were not investigated.

As it seems difficult to proof that the cerebellum is the site of behavioral motor learning, one could maybe show that Purkinje cell activity changes during learning as predicted by the Marr-Albus-Ito theory. An example of this approach are studies on the adaptation of the gain of the vestibulo-ocular reflex (VOR). The change in gain is abolished by lesions of the oldest part of the cerebellum, the flocculus (Ito, 1984). Ito proposed the flocculus hypothesis of motor learning as a specific instance of the Marr-Albus theory (Ito, 1982). It suggests that CF activity would induce changes in Purkinje cell SS activity during VOR adaptation which should be opposite to the changes in gain (because Purkinje cells inhibit the neurons driving the motor reflex). Several experiments seemed to confirm this hypothesis. For example, complex spike activity in the flocculus represents retinal error (Ghelarducci *et al*., 1975) and in some monkey Purkinje cells the changes in simple spike (SS) activity were opposite to the change in VOR gain (Watanabe, 1984). Other experiments suggest that the picture is more complex, as the SS activity in floccular Purkinje cells can also encode retinal error and sometimes the change in SS activity is even similar to the change in gain (Miles *et al*., 1980). This led to a vivid discussion between a group proposing that the site of VOR learning was in the brainstem (Miles and Lisberger, 1981) and Ito (1989)who claimed that these experiments were flawed because the "wrong" Purkinje cells were recorded. Recently Lisberger presented an extensive series of experiments which try to resolve this issue (Lisberger, 1994; Lisberger *et al*., 1994a, b). He found that the same Purkinje cells can change SS activity either in the same or in the opposite direction of the VOR gain, depending on the experimental paradigm used (Lisberger *et al*., 1994a). He proposed a new model in which learning requires changes of inputs to both Purkinje cells and brainstem neurons (Lisberger, 1994). While cerebellar LTD could play some role in these changes, it does not seem very likely as not only the strength but also the timing of the PF inputs must be modified.

A third approach would be to demonstrate that the CF input is an error signal. Again such studies have produced conflicting results. For example, several groups have reported increases in CF firing in decerebrated animals when locomotion on a treadmill is perturbed (Andersson and Armstrong, 1987; Lou and Bloedel, 1992; Yanagihara and Udo, 1994). But while a transient increase in CF firing has been found during the learning of arm movements in awake monkeys, it was not related to any subsequent change in SS firing rate (Ojakangas and Ebner, 1992). In another monkey experiment, the SS firing seemed to be the "error signal", as it increased in half of the recorded Purkinje cells during slip of a hand-held object, while no CS activity was evoked at all (Dugas and Smith, 1992).

A less evident approach has been to investigate changes in SS firing induced by CS activity in the same Purkinje cell, assuming that induction of LTD would cause a decrease in the SS frequency. In some cases an increase in SS firing after the CS was found instead (Ebner *et al*., 1983; Sato *et al*., 1992) or changes were inconsistent (Ojakangas and Ebner, 1992). However, this experimental approach cannot provide any evidence for or against LTD, as such an interpretation of the data would require the unlikely assumption that mossy fiber inputs remained constant during the analysis. Similarly, the increase in the frequency of Purkinje cell SS after destruction of the olivary nucleus (Colin *et al*., 1980) is unlikely to be caused by a

progressive absence of LTD, because such changes were also seen within a few seconds after cooling of the olive (Montaloro *et al*., 1982). A more probable cause of the increase in SS firing rate are changes in other inputs to the Purkinje cells, evoked by the silencing of CF contacts onto inhibitory cortical neurons (Ito, 1984) and onto neurons of the deep cerebellar nuclei (Van Der Want *et al*., 1989).

Finally, many properties of the CF input have been discovered over the last two decades that are not explained by the theories of Marr (1969) and Albus (1971). For example, anatomical studies suggest that CF inputs are organized into 6 or 7 distinct sagittal zones (Voogd and Bigare, 1980), while multi-unit recordings have demonstrated that CF can synchronously activate sagitally aligned Purkinje cells (Sasaki *et al*., 1989; Welsh *et al*., 1995). This has led Bloedel (1992) to suggest that the role of the CF input might be to select functional populations of Purkinje cells by transiently increasing their sensitivity to MF inputs (Ebner *et al*., 1983). Another anatomical finding which is difficult to reconcile with the Marr-Albus-Ito theories are the CF collaterals to neurons in the deep cerebellar nuclei (Van Der Want *et al*., 1989). Similarly, it is not clear how error signals could be generated by the olive, which is in fact a slowly oscillating network (Llinás and Yarom, 1981) that seems to gate excitatory inputs (Lampl and Yarom, 1993) so that the CF fires in phase to the endogenous frequency of about 1 Hz (Sasaki *et al*., 1989). The oscillatory properties of the olivary nucleus have led Llinás and Welsh to propose that the olivocerebellar circuit serves as a clock that is essential for the proper timing of movements (Sugihara *et al*., 1993; Welsh *et al*., 1995). Despite the fact that many authors have proposed alternative theories about the function of the CF input (Bloedel, 1992; Welsh *et al*., 1995), none has made any suggestions about the functional role of cerebellar LTD.

Long-term depression in Purkinje cells

Apart from indirect evidence obtained in extracellular recordings of Purkinje cells *in vivo* (reviewed in Ito (1989)), the first experimental evidence for LTD came from work by Ito and his colleagues in the early eighties (Ito et al., 1982). They claimed to evoke *in vivo* LTD in floccular Purkinje cells by conjunctive stimulation of the inferior olive and the vestibular nerve (MF input). Subsequently, similar results were reported for PF tract stimulation in combination with inferior olive stimulation (Ito and Kano, 1982; Ekerot and Kano, 1989), though others could not reproduce these findings (Llinás *et al*., 1981). In successful experiments, LTD was always restricted to the activated MF (Ito *et al*., 1982) or PF inputs (Ito and Kano, 1982; Ekerot and Kano, 1989). But a large number of conjunctive activations (usually 100 or more at 1 to 4 Hz, the physiological CF frequency) were used to evoke LTD.

The existence of cerebellar LTD remained controversial until the phenomenon was shown to exist in slice preparations (Sakurai, 1987; Crépel and Jaillard, 1991; Konnerth *et al*., 1992) and in cultured Purkinje cells (Hirano, 1990; Linden *et al*., 1991). These preparations have also provided insights into the pharmacological and biochemical properties of LTD. I will only mention facts relevant to the induction of LTD, a complete review can be found in Linden (1994). The expression of cerebellar LTD is probably located entirely at the postsynaptic site. LTD in Purkinje cells can be induced by activation of alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and metabotropic receptors (Ito and Karachot, 1990; Linden *et al*., 1991) in conjunction with an elevated dendritic Ca^{2+} concentration (Sakurai, 1990; Konnerth *et al*., 1992). In the classic scheme, release of glutamate by the PF would activate the AMPA and metabotropic receptors, while the CF input would cause Ca^{2+} influx through voltage-gated dendritic Ca^{2+} channels (Knöpfel *et al*., 1991; Miyakawa *et al*., 1992). However, any mechanism that causes elevated Ca^{2+} concentrations, like depolarization of the Purkinje cell, can induce LTD of activated PF synapses (Crépel and Jaillard, 1991; Linden *et al*., 1991; Konnerth et al., 1992). The Na^{+} influx through the AMPA receptor channel, which may be enhanced by increased activity of the Na^{+}-Ca^{2+} exchanger (Staub *et al*., 1992), may be a necessary co-factor to the induction (Linden *et al*., 1993). Some groups have provided indications that the release of nitric oxide is also needed (Shibuki and Okada, 1991; Daniel *et al*., 1993) or even sufficient in combination with the rise in Ca^{2+} concentration (Lev-Ram *et al*.,

1995) to induce LTD, but this is contradicted by experiments in cell culture (Linden *et al*., 1995) and remains highly controversial (Vincent, 1996).

Much less is known about the extinction of LTD, which seems to be quite variable. Sometimes LTD recovers after 40 min (Sakurai, 1987; Crépel and Jaillard, 1991), but usually it persists for up to several hours (Linden, 1994).

Finally the minimal induction requirements have not been defined. While many researchers use similar stimulation protocols in slice as *in vivo* (i.e. 100 CF activations) (Sakurai, 1987; Schreurs and Alkon, 1993), there is evidence that a smaller number of CF-PF pairings might be sufficient (8 in Cs^{+}-loaded Purkinje cells (Konnerth *et al*., 1992)). In one report, LTD could be evoked in only half of the tested Purkinje cells by strong depolarization in conjunction with 600 PF stimulations at 1 Hz (Crépel and Jaillard, 1991). Data on how much a single PF synapse can be weakened by LTD are not available (though recent technological advances may make such measurements possible (Barbour, 1993)), but the effect on composite EPSPs is relatively weak (a depression of 20 to 50% (Sakurai, 1987; Crépel and Jaillard, 1991; Konnerth *et al*., 1992)).

The induction properties of LTD do not fit the Marr-Albus-Ito theories

The available information suggests that induction of LTD *in vivo* might require conditions which are difficult to reconcile with the Marr-Albus-Ito theories. For example, it is hard to imagine that motor learning in a natural environment would depend on 100 conjunctive CF-PF activations in a minute or less. Many of the differences between the *in vivo* and *in vitro* studies might be explained by the absence of inhibition in the latter, either by pharmacological block (Sakurai, 1987; Crépel and Jaillard, 1991), or by cutting the axons of inhibitory interneurons (Konnerth *et al*., 1992). It is more difficult to induce cerebellar LTD if normal inhibition is present (Ekerot and Kano, 1985; Schreurs and Alkon, 1993). It has been suggested that this effect of inhibition is a stimulus artifact (Ito, 1996), but it is is unlikely that electrical stimulation is the sole cause of the inhibition. First, during on-beam stimulation, as used to activate PF for the induction of LTD, no IPSPs are observed in intracellular recordings, while they are obvious during off-beam stimulation (Ajima and Ito, 1995). Second and more important, whole-cell voltage-clamp recordings of Purkinje cells in slice show the presence of continuous spontaneous inhibitory inputs (Vincent *et al*., 1992). Others have proposed that the inhibitory effect is due to a suppression of the plateau potential that can follow a CS (Ekerot and Kano, 1985), but these plateaus are often absent in experiments where LTD was induced (Sakurai, 1987). Recent Ca^{2+} imaging experiments have demonstrated that inhibition can selectively suppress the Ca^{2+} influx during a CS (Callaway et al., 1995). The interference of inhibition with the induction of LTD has been invoked to explain experiments in which LTD could not be found when the Marr-Albus-Ito theories predicted it should be present (Ito, 1989), but in fact these theories do not provide any explanation why normal inhibition should interfere with motor learning. The new hypothesis (De Schutter, 1995a) provides a simple functional explanation for the interaction between of LTD induction and inhibition.

The most serious problem with using the Marr-Albus-Ito theories to explain the function of LTD, is the required timing of the CF input. To attain maximum depression, the CF input must occur about 10 ms to 100 ms before the PF activation, so that the rise in Ca^{2+} concentration is maximal (Ekerot and Kano, 1989; Schreurs and Alkon, 1993). However, such a sequence is opposite to what classical conditioning and the Marr-Albus theory would suggest, as the "error signal" (the CF) should come after the conditioned stimulus (the PF) (Schreurs and Alkon, 1993). In fact, when the standard timing of the classical conditioning paradigm is used in slice, no LTD is induced (Karachot *et al*., 1994).

Recent experimental evidence suggests that beside the classical CF-induced LTD, one can also induce LTD by PF stimulation alone (N.A. Hartell, 4th IBRO Meeting, Kyoto 1995; G.J. Augustine, personal communication). These findings fit well with recent Ca^{2+}-imaging experiments showing localized increases of the intradendritic Ca^{2+} concentration evoked by focused PF stimulation (Midtgaard *et al*., 1993; Denk *et al*., 1995; Eilers *et al*., 1995) and older reports demonstrating that the CF input is not required to induce LTD (Crépel and Jaillard, 1991; Linden *et al*., 1991; Konnerth *et al*., 1992). PF-induced LTD is possible because the local elevations of Ca^{2+} concentration that coincide with the activation of AMPA and metabotropic receptors are sufficient to induce LTD of the activated PF synapses. This recent experimental evidence contradicts older reports showing that PF stimulation alone could not induce LTD *in vivo* (Ito *et al*., 1982; Ekerot and Kano, 1985). This might again be explained by the fact that LTD is not easy to induce *in vivo*, as 100 to 1000 CF-PF pairings were required to induce cerebellar LTD (Ito *et al*., 1982; Ekerot and Kano, 1985; Ekerot and Kano, 1989).

Other forms of plasticity at Purkinje cell synapses

Adult Purkinje cells lack *N*-methyl-D-aspartate (NMDA) receptors (Farrant and Cull-Candy, 1991; Llano *et al*., 1991b) and consequently classical LTP cannot be induced in these neurons (Artola and Singer, 1993). However, a form of potentiation of PF synapses has been described by several authors (Sakurai, 1987; Hirano, 1990; Crépel and Jaillard, 1991; Schreurs and Alkon, 1993). This potentiation is elicited by 1 to 4 Hz stimulation of PF fibers without CF activation and is more easily obtained if the Purkinje cell is hyperpolarized (Crépel and Jaillard, 1991). Because it decays rapidly over 10 to 50 min (Sakurai, 1987), it is similar to the short term potentiation (STP) of excitatory synapses described in the hippocampus (Malenka and Nicoll, 1993). STP can be induced in CA1 pyramidal cells by activating Ca^{2+} channels (Kullmann *et al*., 1992), without the NMDA receptor activation which seems to be required for LTP induction (Malenka and Nicoll, 1993). A recent report claiming that LTP could be induced in Purkinje cells also described experiments in hyperpolarized cells (Salin *et al*., 1995).

Recently, two groups have reported plasticity of the inhibitory synapses on Purkinje cells (Llano *et al*., 1991a; Kano *et al*., 1992; Vincent *et al*., 1992). Gamma-aminobutyric acid (GABA) receptor-mediated chloride currents are potentiated after short trains of CF activation (Kano *et al*., 1992). Again, the elevation of the intradendritic Ca^{2+} concentration is the important evoking factor and the CF activation can be replaced by depolarization (Llano *et al*., 1991a; Kano *et al*., 1992; Vincent *et al*., 1992). This potentiation seems to be postsynaptic as it applies also to currents evoked by applied GABA (Llano *et al*., 1991a). However, the potentiation is non-specific because it does not require activation of the inhibitory inputs during the depolarization (Llano *et al*., 1991a). It extinguishes in less than an hour (Kano *et al*., 1992; Vincent *et al*., 1992). Unfortunately all these results were obtained in Cs^{+}-loaded Purkinje cells only and confirmation of the plasticity of inhibitory synapses under normal physiological conditions is still lacking.

The control over dendritic spiking in Purkinje cells

Purkinje cells are well known for the marked presence of Ca^{2+} channels in their dendrites, which cause Ca^{2+} dendritic spikes *in vitro* (Llinás and Sugimori, 1980). Purkinje cells often burst in slice recordings, sometimes spontaneously or during current injection (Llinás and Sugimori, 1980). When inhibition is completely blocked in cerebellar slices by application of picrotoxin, most adult Purkinje cells burst continuously (Jaeger and Bower, 1994).

Purkinje cells *in vivo*, however, never generate large dendritic Ca^{2+} spikes under normal conditions, except during a complex spike caused by a CF input (Armstrong and Rawson, 1979; Montaloro *et al*., 1982). They fire simple somatic spikes at a fast, stochastic rhythm of 30 to 100 Hz (Murphy and Sabah, 1971; Armstrong and Rawson, 1979).

The firing properties of these neurons are therefore quite different depending on whether one records activity in the slice preparation or *in vivo*. These differences are probably caused by the presence of background excitatory and inhibitory inputs *in vivo*. The effect of continuous synaptic activation was investigated with a large, detailed computer model of the Purkinje cell (De Schutter and Bower, 1994a). The results of these simulations are summarized in Fig. 2. The model reproduced the normal somatic firing pattern of Purkinje cells *in vitro*, which is a mixture of simple spikes and dendritic spikes (Fig. 2A). When only random PF excitation was applied to the model it burst continuously (Fig. 2B). This was caused by the large number of PF inputs (Harvey and Napper, 1991) and by the low activation threshold of the dendritic P-type Ca^{2+} channels (Regan, 1991; Llinás and Sugimori, 1992). Very low rates of PF excitation caused a fast, regular firing of simple spikes (De Schutter and Bower, 1994b). Neither of these firing patterns is ever observed *in vivo* (Murphy and Sabah, 1971; Armstrong and Rawson, 1979) and in both patterns the firing frequency was relatively independent of the PF input frequency (De Schutter and Bower, 1994b). However, if random stellate cell inhibition was combined with PF excitation, a normal irregular firing pattern was obtained (Fig. 2C) and the firing frequency became very sensitive to small changes in PF input frequency. These simulations suggest that *in vivo* dendritic spikes are actively suppressed by inhibition (De Schutter and Bower, 1994b). This prediction was confirmed by intracellular recordings from Purkinje cells *in vivo*, where application of the GABAA receptor blocker bicuculline caused these cells to burst spontaneously (Jaeger and Bower, 1994).

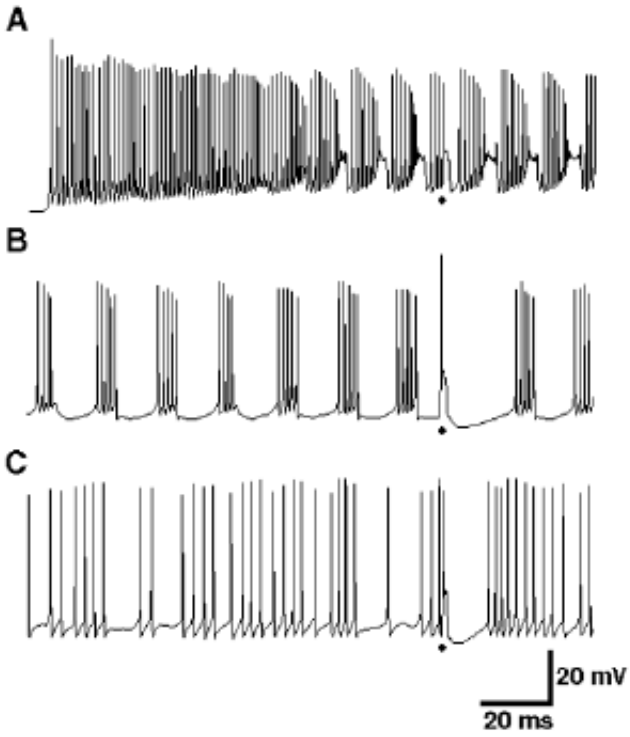

Fig. 2: Computer simulation of Purkinje cell somatic firing patterns *in vitro* and *in vivo*. A CF input causes a complex spike towards the end of each trace (CF activation marked by *). (**A**) Firing pattern in the slice preparation caused by 2 nA current injection in the soma. Initially the cell fires only simple spikes, subsequently dendritic Ca^{2+} spikes appear. (**B**) Firing pattern when only asynchronous PF inputs are provided to the model. The cell bursts continuously in a highly repetitive manner. This firing pattern is caused by dendritic spikes and can be recorded *in vivo* when inhibition is blocked. (**C**) Firing pattern when both asynchronous PF and inhibitory inputs are provided to the model. The cell fires an irregular rhythm consisting only of simples spikes, except after the CF input. This is the normal *in vivo* firing pattern.

This evidence indicates that the role of dendritic Ca^{2+} channels of Purkinje cells *in vivo* is not to generate large dendritric Ca^{2+} spikes. Instead they may play an important role in amplifying PF inputs *in vivo* (Llinás and Sugimori, 1992; De Schutter, 1994; De Schutter and Bower, 1994c) and in providing a mechanism for background PF inputs to interact with coherent input (De Schutter, 1995b). The computer model shows that the activation of dendritic Ca^{2+} channels required for these amplification mechanisms (De Schutter and Bower, 1994c) is similar to that observed experimentally (Eilers *et al*., 1995) and does not result in the appearance of burst activity in the firing pattern.

A new hypothesis: LTD as a local feedback process

While numerous aspects of LTD remain poorly described, there can be no doubt of its existence. But, for

reasons mentioned above, it is not evident that this change in synaptic strength could function as a memory trace within the framework of the Marr-Albus-Ito theories. While some researchers have tried to adapt these theories, for example by giving the olivary inputs a different role (Houk *et al*., 1990), it seems more useful to consider whether LTD could have a completely different function in the cerebellar circuitry.

In my review of LTD and Purkinje cell properties, I have discussed several facts which together point to such an alternative theory. To recapitulate, continuous strong inhibition of Purkinje cells is essential to suppress dendritic spikes *in vivo* (Fig. 2) and to maintain a simple spike firing pattern which is sensitive to changes in PF input frequency (De Schutter and Bower, 1994b). Therefore it is likely that the suppression of spontaneously generated dendritic spikes by inhibitory neurons is important for the normal function of Purkinje cells *in vivo*. However, the cerebellum seems maladapted to maintain this suppression of dendritic spikes as it lacks any circuitry that can provide local negative feedback. If a particular region of a Purkinje cell dendrite is being overstimulated, there is a need for a feedback mechanism that can increase the inhibitory drive, reduce the amount of excitatory input, or both. Without such a mechanism, a mismatch between inhibition and excitation onto an individual Purkinje cell would cause the neuron to fire Ca^{2+} spikes if the rate of excitation is too high, or if there is too much inhibition the cell would not fire at all (De Schutter and Bower, 1994b) .

Actually, negative feedback does exist in the cerebellum, but not at the circuit level. The PF-induced LTD and the other forms of Purkinje cell synaptic plasticity all have properties which make then suitable to implement the required feedback, albeit at a slower time scale than that usually associated with control mechanisms. The way in which this plasticity-induced feedback would work is presented in Fig. 3. Let's assume that an overexcitation caused by a lack of sufficient inhibition, results in a large depolarization of parts of the dendrite (Fig. 3A). This depolarization will open voltage-gated Ca^{2+} channels and the local Ca^{2+} concentration will rise whenever the PF inputs are active. First, this increased Ca^{2+} concentration will potentiate all inhibitory inputs onto that region of the dendrite. Next, if the Ca^{2+} concentration repeatedly crosses a certain (unknown) threshold, LTD of the active PF inputs will be induced (Fig. 3B). This will eventually result in a net reduction of the excitatory drive on that part of the Purkinje cell dendrite so that much less voltage-gated Ca^{2+} channels are activated whenever the local PF input fires. This diminishes the chance of triggering a dendritic spike and at the same time the Ca^{2+} concentration will remain within normal levels. The opposite could happen if inhibition is too strong. Though the induction properties of STP in Purkinje cells have not been studied, it seems likely that STP will occur if a high rate of PF activation does not cause a minimal depolarization evoking at the same time a small increase in Ca^{2+} concentration. Thus, if excitation is not effective, active PF inputs will be potentiated and at the same time potentiation of inhibitory inputs will decrease.

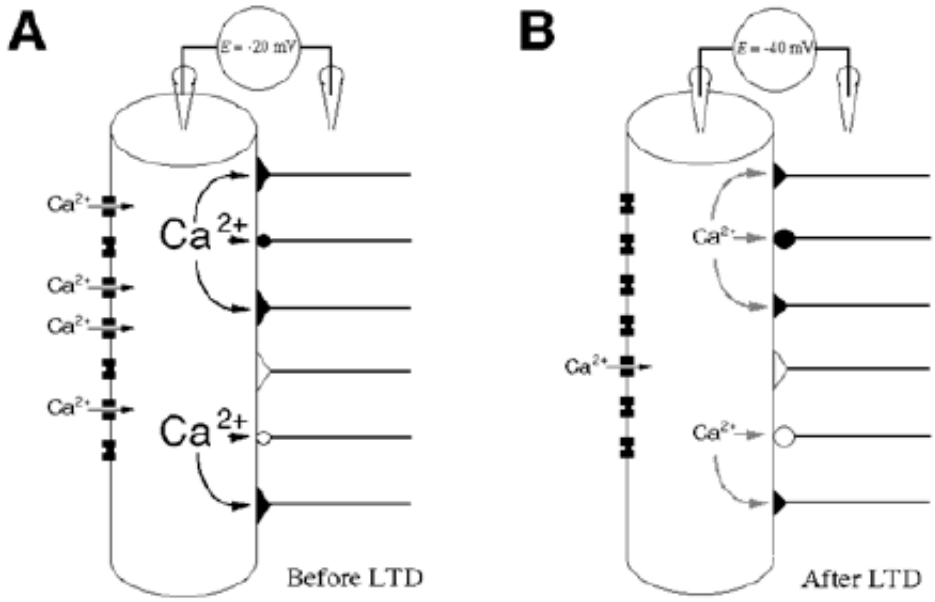

Fig. 3: Schematic illustration of LTD and potentiation of inhibitory inputs as a local negative feedback process. A small part of a Purkinje cell dendrite is shown. PF synapses are represented by triangles and inhibitory synapses by circles, black synapses are active. (**A**) The dendrite is being overstimulated by the co-activation of several PF inputs. This results in a depolarization and Ca^{2+} inflow. The increase in Ca^{2+} concentration will cause potentiation of all inhibitory synapses and eventually induce LTD of the active PF synapses, resulting in the situation shown in (**B**) Now co-activation of the same, depressed PF synapses combined with the potentiated inhibitory inputs cause a much smaller depolarization and only a small increase in the Ca^{2+} concentration, insufficient to induce any additional changes in synaptic strength.

Because not much is known about the detailed induction and extinction kinetics of LTD (Linden, 1994) and STP (Sakurai, 1987), it is difficult to predict in the context of this hypothesis the timescales over which cerebellar LTD and STP will occur *in vivo*. One possibility is that LTD is a gradual process, with the amount of weakening correlated to the Ca^{2+} level beyond a certain threshold, and with a relatively fast extinction (Sakurai, 1987). In that case, one would predict that LTD is part of a dynamic equilibrium which adapts continuously to slow changes in excitation patterns. In the opposite case, where depression tends to reach a low, fixed synaptic strength and show little extinction, one would expect LTD to be induced mainly during early life, until a stable equilibrium is reached. In this context it is interesting to note that LTD investigations are often performed on Purkinje cells from fetal (Linden *et al*., 1991) or juvenile (Crépel and Jaillard, 1991; Konnerth *et al*., 1992) animals.

The new hypothesis does not provide any specific function to the CF input. Based on the arguments presented earlier, it could be argued that CF-induced LTD does not occur under normal *in vivo* conditions because too may co-activations with the same PF inputs are required (Ito *et al*., 1982; Ekerot and Kano, 1985; Ekerot and Kano, 1989). However, at this time we do not know enough about the quantitative requirements for the induction of any form of cerebellar LTD. More experiments are needed to resolve this issue and to explore the functional role of PF-induced LTD (De Schutter, 1995a).

The hypothesis presented in this chapter proposes that LTD is part of a local regulatory mechanism, required for normal Purkinje cell function. A consequence of this hypothesis is that locally controlled changes in the gain of PF synapses should not interfere with the function of the cerebellar cortex, which is in contrast to the Marr-Albus-Ito theories where PF synaptic strengths encode learned information. But if motor learning is not the function of Purkinje cells and the cerebellum, then what could it be? Recent experimental evidence suggests that the human cerebellum may also be involved in cognitive and language functions (Leiner *et al*., 1989) and Bower presents in this volume evidence for a role in the control over sensory acquisition. Based on fractured somatotopy of MF inputs (Shambes *et al*., 1978; Bower and Kassel, 1990) and on our own modeling work (De Schutter, 1994; De Schutter and Bower, 1994b) we have proposed that the Purkinje cell can operate as a filter which is responsive to fast variations in PF input activity, while the slower changes in PF frequency that are canceled by feedforward inhibition change the gain of the filter (De Schutter and Bower, 1993; De Schutter, 1995b). If Purkinje cells indeed operate as temporal filters, they would be much less sensitive to the synaptic strength of PF inputs.

In conclusion, the synaptic plasticity of PF and inhibitory synapses may not be a memory trace at all, but instead might provide a local feedback mechanism. This mechanism regulates the total excitation of the Purkinje cell at a level of depolarization where the simple spike firing rhythm is maximally responsive to changes in PF input and where no full-blown dendritic Ca^{2+} spikes are generated (De Schutter and Bower, 1994b). The feedback process is controlled by the dendritic Ca^{2+} concentration, which is an indicator of the level of depolarization caused by synaptic input. The longer persistence of LTD compared to STP of PF synapses suggests that preventing overstimulation is more important in this system, which has the largest convergence of excitatory inputs in the mammalian brain (Ito, 1984; Harvey and Napper, 1991).

ACKNOWLEDGEMENTS

I wish to thank David J. Perkel, Michael Lyons and Dieter Jaeger for their helpful comments on early versions of this manuscript. My work is supported by NFWO (Belgium), by HFSPO and by NIH RO1-MH52903.

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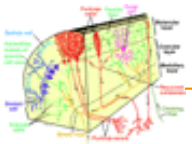

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