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The cerebellum: cortical processing and theory **Erik De Schutter**, **Reinoud Maex**

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ABSTRACT

Several advances over the past year have made a complete reevaluation of the function of the cerebellum and of the role of cerebellar synaptic plasticity necessary. These include the discovery of parallel fiber-induced long term depression, the lack of effect on motor coordination of the absence of cerebellar long term depression in knockout mice and the strong activation of the cerebellar nuclei during sensory tasks.

Introduction

These are exciting times for cerebellar research. The field has been dominated for several decades by two dogmas. The first one is that the cerebellum is exclusively involved in motor control. The second dogma, the theory of cerebellar motor learning first proposed by Marr [1] and Albus [2] and subsequently elaborated by Ito [3] and others, is more controversial. Standard textbooks may give the impression that this theory has been confirmed by classical conditioning experiments [4] and hence became generally accepted, but large parts of the cerebellar research community have never believed the cerebellum to be the site of memory storage for motor learning [5-6, **7].

The Marr-Albus-Ito theory proposes that only a subset of the more than 150,000 parallel fiber (PF) synapses [8] contacting any particular Purkinje cell (PC) controls its output and ultimately the motor system. This would be accomplished by weakening the strength of the PF synapses activated during an erroneous motor command. The error signal leading to such weakening was proposed to be the climbing fiber (CF) input causing a complex spike in the PC. In other words, conjunctive activation of CF and PF synapses should lead to a reduced strength of the PF synapse, a process called long-term depression (LTD) [9].

Both dogmas are now being challenged by recent experimental findings.

LTD and the timing of the CF input

The Marr-Albus-Ito theory critically depends on the conjunctive nature of CF-induced LTD (CF-LTD). The CF input activates dendritic and somatic calcium channels leading to calcium influx [10, 11] which induces LTD of the activated PF synapses [9]. Many groups have demonstrated that an increased dendritic calcium concentration is sufficient to induce LTD; the CF input itself is not necessary (reviewed in [**7]). But if CF input is used, LTD is induced in cerebellar slices solely if the CF input precedes or coincides with the PF input [12]. Only the CF->PF sequence of activation leads to an increased dendritic calcium concentration during the PF input, but it is opposite to what would be expected if the CF signals an error in motor performance linked to the PF-activation. Neither does it conform to the order in classical conditioning experiments, where the conditioned stimulus (PF input) precedes the unconditioned stimulus (CF input) [4, 12]

It has been known for quite some time that a CF->PF sequence is needed for LTD-induction in slice [**7], which has led some theoreticians to propose unsubstantiated alternative induction schemes [13]. Many researchers, however, seem to find the results from classical conditioning experiments [4] more convincing than

the slice experiments [**7, 12]. This is exemplified in a model of the biochemical pathways responsible for the induction of LTD in PCs [14], which depends on release of calcium from inositol triphosphate (IP3) sensitive stores [15] to learn particular time intervals between the PF and the CF input [14, 16]. This supposedly realistic model shows LTD induction for the PF-CF sequence [14] which is ineffective in slice [12]. Moreover it is unclear how robust the model would be to noisy input.

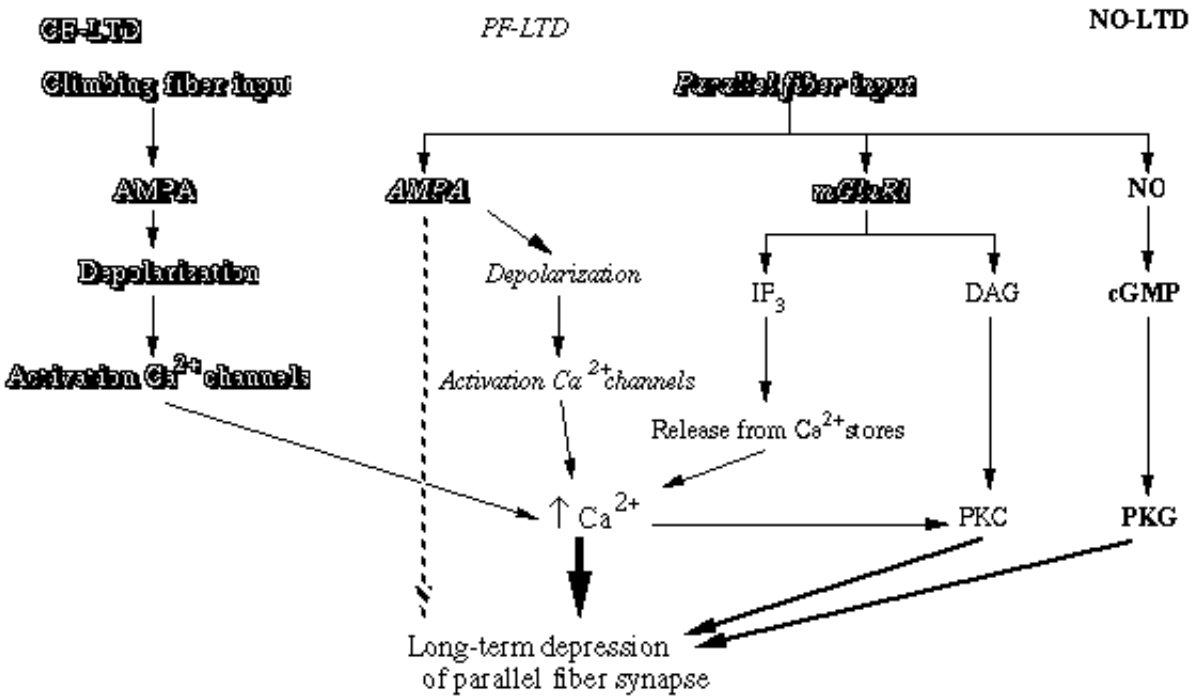

Fig. 1: Schematic representation of the pathways thought to be involved in the induction of three forms of LTD of PF synapses in PCs. Each pathways is coded by shadow (CF-LTD), italic (PF-LTD) or bold (NO-LTD) print. Note that these pathways may overlap to a large degree, e.g. CF-LTD requires activation of the AMPA and mGluR1 receptors of the PF synapse [9]. There are contradictory reports on whether the same holds true for NO-LTD [**21, *24], but it is likely that PKG activity alone (without PKC) is insufficient [25]. Activation of the AMPA receptor of the PF synapse is needed to induce CF-LTD (and PF-LTD), but the exact pathways involved are unknown (Na^+ influx through the receptor might be important [9]). It has not been demonstrated that mGluR1 activation is necessary for induction of PF-LTD, but this seems likely. Finally, it is quite possible that all these pathways are activated together to variable degrees during experiments which use conjunctive CF-PF stimuli to induce LTD. Abbreviations (see also text): DAG = 1,2 diacylglycerol; PKC = protein kinase C; PKG = protein kinase G.

Three forms of cerebellar LTD

One of the questions with CF-LTD was how a CF input on the smooth dendrite can raise the calcium concentration close to the PF synapses located on the spiny dendrite. This was solved when calcium imaging experiments demonstrated that the complex spike causes activation of voltage-gated calcium channels everywhere in the dendritic tree [10], including the spiny dendrite. Computer modeling showed that localized PF inputs should also activate calcium channels [17] because of the high density of these channels in the spiny dendrite. This prediction was recently confirmed by two groups [**18, *19]. Eilers *et al.* [**18] used confocal laser scanning microscopy to show that small focal PF inputs lead to transient localized increases in the dendritic calcium concentration, proportional to the size of the PF stimulus. Another study using two-photon excitation imaging demonstrated that even a single PF input activates calcium channels located on the dendritic spine [*19]. Additionally, a subset of PF synapses was found where calcium influx through the AMPA

receptor channel might be a second source of increased calcium [*19]. More quantitative studies suggest, however, that the calcium fraction of the total synaptic current through AMPA receptor channels is less than 1% in PCs [20].

Whatever the contribution of calcium influx through synaptic channels, focal PF activation can lead to local calcium influx. As was pointed out by us [**7], this PF-induced calcium inflow fulfills the biophysical requirements for the induction of LTD of the activated synapses (PF-LTD). The existence of PF-LTD has recently been confirmed experimentally [**21]. PF stimulation at strengths sufficient to cause calcium inflow similar to that demonstrated by Eilers et al. [**18] induced a LTD of the activated PF synapses which largely occluded further depression by CF-LTD [**21]. Interestingly, under the same experimental conditions a second form of LTD was induced. This nitric oxide-dependent LTD (NO-LTD) affected PF synapses presumably not activated during the stimulus presentation. The role of NO in cerebellar LTD has been controversial for some time [9, 22] as NO synthase is notably absent in PCs and in the CFs which were assumed to release it [23]. Neuronal NO synthase is, however, present in PFs [23] and one study claims that NO application can replace the PF input in LTD induction [*24]. There remain important issues to be resolved, like whether the NO application needs to be combined with an increased postsynaptic calcium concentration [*24] or not [**21, 25], if activated PFs always release NO and how NO-LTD interacts with CF-LTD [25].

As summarized in Fig. 1, we may now distinguish three forms of LTD at the PF synapse. CF-LTD, the `Marr-Albus-Ito form', is conjunctive and specific to the activated PF synapses. PF-LTD is non-conjunctive but also specific; while NO-LTD is maybe conjunctive but also diffuse, affecting distant non-activated PF synapses. Moreover, PF-LTD is more easibly induced in cerebellar slices than CF-LTD (Hartell, personal communication). In our opinion, the existence of PF-LTD and NO-LTD is an even more serious objection to the Marr-Albus-Ito theory of cerebellar learning than the CF->PF sequence needed for CF-LTD. It is indeed difficult to imagine how a non-conjunctive change in synaptic plasticity can co-exist with learning through conjunctive CF-LTD, as the PF-LTD would occlude learned patterns [**21].

If cerebellar LTD is not a mechanism for motor learning, what is then its function? We have recently proposed that LTD of the PF synapse, complemented by the potentiation of inhibitory synapses on PCs [26], might be important in normalizing the total excitatory input onto a single PC [**7]. The typical circuitry of the cerebellum does not provide for a feedback mechanism to regulate the balance between excitation and inhibition onto PCs. It seems that such a regulation would be essential in a cell which receives more than 150,000 excitatory inputs [8] onto a highly excitable dendrite [**18, *19]. PF-LTD [**21] can provide such an autoregulatory mechanism by slowly reducing the strength of PF synapses when excessive excitation of a PC dendrite leads to calcium influx [**7].

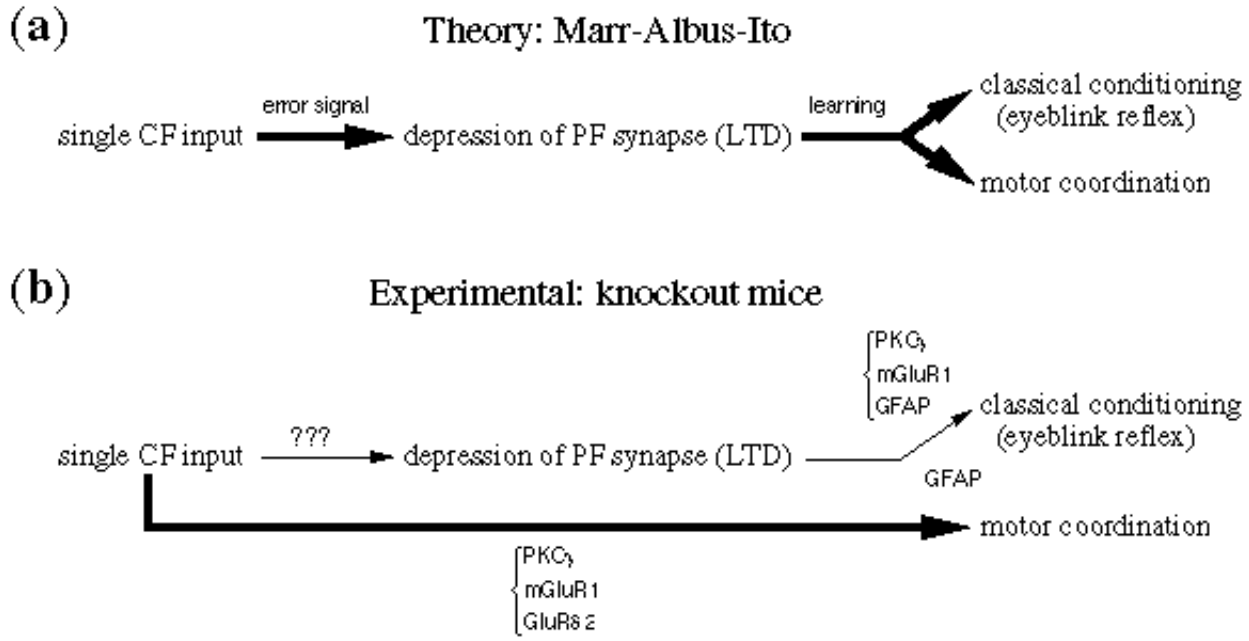

Fig. 2: A comparison between (**A**) the predictions made by the Marr-Albus-Ito theory of cerebellar motor learning and (**B**) the performance of knockout mice on tests of motor coordination and conditioning of the eyeblink reflex. The abbreviations in (**B**) refer to the mutant gene (see text) and the causal effects the specific knockout mice establish or disprove. Important differences between (**A**) and (**B**) are the strong dependence of motor function on single CF inputs, the weak link between LTD and classical conditioning and the absent connection between cerebellar LTD and motor coordination (GFAP mutant). It is unclear if the persistence of multiple CF inputs changes the properties of cerebellar LTD.

Knockout of classical conditioning

Thompson and others have proposed that classical conditioning of the eyeblink reflex is experimental proof that the cerebellum is the memory site of motor learning [4, 16, 27] This work, which is largely based on lesion studies [27], is very controversial [5, 6, 28]. Available space does not allow us to reiterate these criticisms, but recent results from gene targeting experiments shed new light on this issue. The interpretation of motor performance and behavior in knockout mice is, however, complicated by the use of embryonic stem cells derived from a neurologically impaired strain of mice [*29]. Therefore we will mainly compare different knockout experiments instead of considering the function of specific genes.

Over the last two years several mutants with impaired cerebellar LTD have been described. These include knockouts of genes encoding for metabotropic glutamate receptor type 1 (mGluR1) [30, 31], for the glutamate receptor d subunit (GluRd2) [32] and for glial fibrillary acidic protein (GFAP) [33]. Surprisingly, knockouts of protein kinase C gamma (PKC gamma), an enzyme necessary for the induction of LTD [9], did not show reduced LTD [**34]. More important is that three of these mutant strains (mGluR1, GluRd2 and PKC gamma) showed persistent multiple CF innervation of PCs [35]. In normal rodents PCs are innervated by three to four CFs at postnatal day five. The supernumerary CFs are eliminated during the second and third postnatal weeks [36], resulting in a one-to-one relation between CFs and PCs at the age when rodents show adult motor behavior. These three mutants showed severe deficits in motor coordination [30-32, **34], while the GFAP mutant with normal CF innervation did not [33]. The mutants with impaired cerebellar LTD showed reduced learning of the eyeblink reflex [30, 33], but these deficits are only partial and it remains to be proven [**7] that they are caused solely by the absence [30] or decrease [33] of LTD. In this context the PKC gamma mutant may be more illuminating. It showed normal cerebellar LTD and normal, even facilitated, eyeblink conditioning, but severely impaired motor coordination [**34]. These results, which are summarized in Fig. 2, suggest that the one-to-one relation between CFs and PCs is much more important than LTD for the normal

motor function of the cerebellum. The GFAP and PKC gamma mutants suggest that LTD deficits and impaired eyeblink conditioning have very little impact on the motor behavior of the animal.

The mysterious function of the CF input

The results just described demonstrate the importance of the single CF input to PCs. But if this input is not the teacher in motor learning as suggested by Marr [1] and Albus [2], what is then its function [37]? Llinás and co-workers have proposed that the CF is a clock which activates the proper PC assemblies at the right time [38, *39, 40]. Using multiple-microelectrode recordings of PCs they showed that the spatial and temporal organization of CF inputs is rhythmic and time-locked to motor activity [*39]. Synchronous CF inputs show complex spatial patterns which change during sequences of movements. The authors conclude that these spatiotemporal activation patterns allow the control of individual muscles. It remains to be demonstrated, however, that CF activations in this area of the cerebellum are not just a reflection of sensory input instead of motor command signals [*41]. It looks as if some of their results may be species specific, as rhythmic activation of CF inputs was not found in monkeys [42]. Similarly, this group has reported that the conduction time in rat CFs is independent of their length [38] supporting the clock-like synchronous arrival of CF signals everywhere in the cortex [40], but this result was not confirmed in cats [43].

Brain mapping of new cerebellar functions

If it is unclear how the cerebellum works, do we at least understand its function? Recent human brain mapping results suggest we do not, as the cerebellum is activated during many cognitive and language tasks without overt motor components [44], though some argue that some subconscious contribution of the motor system must be involved [45]. A recent functional MRI study [**46] increases the challenge to any theory claiming an exclusive motor function for the cerebellum [45]. This study, which was specifically designed to test Bower's hypothesis that the cerebellum controls sensory acquisition instead of motor function [*41], confirms and extends older PET-studies [47]. Dentate nucleus activity was increased whenever the subject had to make either a passive or active tactile discrimination [**46]. Conversely, the lowest activity was present during a pure motor task. Bower interprets this as evidence that the cerebellum tunes sensory systems, sometimes through activation of the motor system, to improve perception [*41]. Similarly, increased activation of the cerebellar vermis during explicit learning of a visuomotor task could be interpreted as an optimization of visual sensory acquisition [48-49]. Interestingly, suppression of (badly tuned ?) sensory input may reduce tremors in cerebellar patients [50].

Conclusion

In our opinion, the implications of recent findings on the properties of cerebellar LTD [**21] and the lack of correlation between deficient eyeblink conditioning and motor dysfunction [33] are too fundamental to retain the Marr-Albus-Ito theory. Attempts to redefine the theory of cerebellar motor learning [13, 51] fail to account for these findings and lack the clarity and detail of the original theories. New theories are needed, which may be found more easily by a bottom-up approach where first the physiological properties of cerebellar neurons are elucidated. Our detailed computer modeling of the PC [17, 52], for example, has led us to propose a new theory on the role of cerebellar synaptic plasticity [**7].

Such an approach will prevent the use of inappropriate metaphores from computer technology [44, 51] when a new unifying theoretical framework is formulated to explain the cerebellar contribution to motor [6, 53], sensory [**46], cognitive [44] and even autonomic [54] functions. But this will require more refined experimental studies to provide a better understanding of how, for example, motor control is executed by the brain [55].

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