

- 9 Rutkowski, J.L. *et al.* (1995) *Nature Med.* 1, 80–83
- 10 Levi, A.D.O. *et al.* (1995) *J. Neurosci.* 15, 1329–1340
- 11 Avellana-Adalid, V. *et al.* (1995) *Axonal Regrowth in the Mammalian Spinal Cord and Peripheral Nerve, IRME Workshop Abstr.*
- 12 Felts, P.A. and Smith, K.J. (1992) *Brain Res.* 574, 178–192
- 13 Franklin, R.J.M. and Blakemore, W.F. (1995) *Trends Neurosci.* 18, 151–156
- 14 Bogler, O. *et al.* (1990) *Proc. Natl Acad. Sci. USA* 87, 6368–6372
- 15 Louis, J.-C. *et al.* (1992) *J. Neurosci. Res.* 31, 193–204
- 16 Groves, A.K. *et al.* (1993) *Nature* 362, 453–455
- 17 Tontsch, U. *et al.* (1994) *Proc. Natl Acad. Sci. USA* 91, 11616–11620
- 18 Almazan, G. and McKay, R. (1992) *Brain Res.* 579, 234–245
- 19 Kitchens, D.L., Snyder, E.Y. and Gottlieb, D.I. (1994) *J. Neurobiol.* 25, 797–807
- 20 Duncan, I.D., Archer, D.R. and Hammang, J.P. (1993) *Soc. Neurosci. Abstr.* 19, 689
- 21 Avellana-Adalid, V. *et al.* (1994) *Soc. Neurosci. Abstr.* 20, 885
- 22 Yu, W.P. *et al.* (1994) *Neuron* 12, 1353–1362
- 23 Weidenheim, K.M. *et al.* (1993) *J. Neurocytol.* 22, 507–516
- 24 Aloisi, F. *et al.* (1992) *Glia* 5, 171–181
- 25 Satoh, J. and Kim, S.U. (1994) *J. Neurosci. Res.* 39, 260–272
- 26 Noble, M., Wren, D. and Wolswijk, G. (1992) *Semin. Cell Biol.* 3, 413–422
- 27 Gogate, N. *et al.* (1994) *J. Neurosci.* 14, 4571–4587
- 28 Yao, D.L. *et al.* *Proc. Natl Acad. Sci. USA* (in press)
- 29 Carson, M.J. *et al.* (1993) *Neuron* 10, 729–740
- 30 Barres, B.A. and Raff, M.C. (1994) *Neuron* 12, 935–942
- 31 Yasuda, T. *et al.* (1995) *J. Neurosci. Res.* 40, 306–317
- 32 Hopkins, S.J. and Rothwell, N.J. (1995) *Trends Neurosci.* 18, 83–88
- 33 Hopkins, S.J. and Rothwell, N.J. (1995) *Trends Neurosci.* 18, 130–136
- 34 Zajicek, J.P. *et al.* (1992) *Brain* 115, 1611–1631
- 35 Mayer, M. and Noble, M. (1994) *Proc. Natl Acad. Sci. USA* 91, 7496–7500
- 36 Wilt, S. *et al.* (1995) *Ann. Neurol.* 37, 381–394
- 37 Bruck, W. *et al.* (1994) *Ann. Neurol.* 35, 65–73
- 38 Ruddle, N.H. *et al.* (1990) *J. Exp. Med.* 172, 1193–1200
- 39 Sommer, N. *et al.* (1995) *Nature Med.* 1, 244–248

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## VIEWPOINT

## Cerebellar long-term depression might normalize excitation of Purkinje cells: a hypothesis

Erik De Schutter

**Long-term depression (LTD) of parallel-fibre (PF) synapses on Purkinje cells is usually interpreted in the context of a specific theory of motor learning by the cerebellum proposed by Marr, Albus and Ito. Several arguments suggest that this theory might be false. A new hypothesis about the role of cerebellar LTD proposes that, under physiological conditions, LTD is autoinduced by PF inputs. This proposal is based on the capacity of PF inputs to trigger influx of Ca<sup>2+</sup> into the dendrite. Long-term depression and other forms of Purkinje-cell synaptic plasticity are part of a local negative feedback loop that prevents overstimulation of Purkinje cells by PF inputs. This theory explains why it is difficult to induce LTD when a normal level of inhibition is present, and why inhibitory inputs are potentiated by the same conditions that can induce LTD of PF synapses.**

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SINCE HEBB PROPOSED that synaptic modification, based on the co-occurrence of pre- and postsynaptic activity, underlies learning<sup>1</sup>, it has been assumed generally that synaptic plasticity plays a fundamental role in memory. Similarly, long-term depression (LTD) of the parallel-fibre (PF) to Purkinje-cell (P-cell) synapse<sup>2</sup> is an essential component of an influential theory of motor learning by the cerebellum. This theory was first formulated by Marr<sup>3</sup> and elaborated subsequently by Albus<sup>4</sup> and Ito<sup>5</sup>. The differences in how each of the Marr–Albus–Ito theories (MAIT) account for implementation of motor control by the cerebellum are beyond the scope of this viewpoint, but all MAIT assume that the cerebellum learns by storing memory traces at the PF synapse. The olivary nucleus

would control this learning process, because the single climbing fibre (CF) impinging on a P-cell needs to be co-activated repeatedly with a PF synapse to induce LTD. Before learning, many sensory inputs that are carried by mossy fibres (MF) would be able to activate a particular P-cell. However, if this resulted in an error in motor performance, the CF would be activated, leading to weakening of the PF input.

These theories have always been controversial but most of the arguments have focused either on the existence of LTD itself<sup>6,7</sup> before it was demonstrated convincingly in slice experiments<sup>8</sup>, or on the role of the cerebellum in motor learning<sup>5,9</sup>. There is ample evidence that cerebellar LTD is distinct from forms of LTD that are expressed in hippocampus and cerebral cortex. For example, cerebellar LTD has a different

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dependence on the postsynaptic concentration of  $\text{Ca}^{2+}$  (Ref. 2). Moreover, the P-cell is the only neurone where LTD is present without long-term potentiation<sup>10</sup> (LTP), because adult P-cells lack NMDA receptors<sup>11,12</sup>. Consequently, I will assume that cerebellar LTD has a different function to that of LTD in other brain structures.

Several arguments suggest that MAIT are not correct. For example, it has not been possible to prove that motor learning takes place in the cerebellar cortex. It was hoped that studies of the deficits that follow lesions might identify the synapses that are involved in learning during the classical conditioning of simple motor acts but, after many years of study, the results are inconclusive, and opposite conclusions are drawn from similar experiments by different groups<sup>13–17</sup>. This can be explained by the intrinsic difficulties in distinguishing performance deficits from learning deficits<sup>9</sup>, and by variations in the location and extent of the lesions.

Recently, techniques to knockout genes in mice were used to study the function of LTD. Long-term depression is absent in mutant mice<sup>18,19</sup> that lack a specific metabotropic glutamate-receptor subtype<sup>20</sup>. Such mutants can learn the classical conditioning of the eye blink reflex as well as normal animals can during the first three days of training but on the fourth and fifth day, the mutant animals learn significantly less<sup>18</sup>. Aiba and colleagues consider this to be a demonstration of the role of cerebellar LTD in associative motor learning. However, it could also be argued that LTD is not involved in associative learning, as the mutant animals learned normally during the first three days. Moreover, as these animals also show reduced hippocampal LTP (Ref. 21), synaptic-plasticity deficits in another brain structure might have been the cause of the late learning deficit. The motor-control deficits in the mutants are similar to the clinical symptoms of cerebellar lesions<sup>22</sup>, and are probably caused by the absence of cerebellar LTD. For example, the mutant mice are quite ataxic, have impaired walking<sup>18,19</sup>, and perform badly on tests of balance<sup>18</sup>. However, they groom normally<sup>21</sup> and they can swim<sup>19</sup>. This suggests that the motor deficits in these animals are complex, affecting some behaviours more than others.

Another approach to exploring the role of cerebellar LTD is to study the changes in P-cell activity during learning. A popular model is the adaptation of gain of the vestibulo-ocular reflex (VOR), which is abolished by lesions of the oldest part of the cerebellum, the flocculus<sup>3</sup>. Ito studied this example of motor learning extensively, and proposed the flocculus hypothesis as a specific example of MAIT (Ref. 23). Several experiments seemed to confirm this theory. For example, complex-spike (CS) activity in floccular P-cells represents retinal error<sup>24</sup> and, in monkeys, some P-cells show changes in simple-spike (SS) activity similar to the change in VOR gain<sup>25</sup>. However, the SS activity in floccular P-cells can also encode retinal error and, in other experiments, the change in SS activity is opposite to the change in gain<sup>26</sup>. This led Miles and Lisberger to propose that the site of VOR learning was in the brainstem<sup>27</sup>, while Ito claimed that their experiments were flawed because the 'wrong' P-cells were recorded<sup>7</sup>. Recently, Lisberger showed that the same P-cells can change SS

activity either in the same or in the opposite direction of the VOR gain, depending on the experimental paradigm used<sup>28</sup>. On the basis of extensive recordings, a new model was proposed in which learning requires changes of inputs to both P-cells and brainstem neurones<sup>29</sup>. This hypothesis is quite different from MAIT because both the synaptic strength and the timing of the MF inputs must be changed. It is an attractive model because it simulates neuronal activity during both VOR learning and smooth visual pursuit.

Studies of the CF as a possible error signal in other parts of the cerebellum have produced conflicting results. Several groups have reported increases in CF firing in decerebrated animals when locomotion on a treadmill is perturbed<sup>30–32</sup>, but these CSs do not seem to induce LTD as SS firing is increased after the CS (Ref. 31). Similarly, P-cell responsiveness to MF input is enhanced after spontaneous CSs (Refs 33 and 34). In awake monkeys, a transient increase in CF firing is present during the learning of arm movements, but it is not related to any subsequent change in SS-firing rate<sup>35</sup>. In another experiment, the SS firing seems to be the 'error signal', as it increases in 49% of recorded monkey P-cells during slip of a hand-held object, while no CS activity is elicited<sup>36</sup>.

Since Marr<sup>3</sup> and Albus<sup>4</sup> published their theories, many properties of the CF input have been discovered that are not explained by MAIT. For example, anatomical studies suggest that CF inputs are organized into six or seven distinct sagittal zones<sup>37</sup>, while multi-unit recordings show that CF can activate sagittally aligned P-cells synchronously<sup>38</sup>. This has led Bloedel<sup>9,31</sup> to suggest that CF inputs select functional populations of P-cells by increasing their sensitivity to MF inputs transiently<sup>33</sup>. The olivary nucleus has been shown to be a coupled, slowly oscillating network<sup>39</sup>. Excitatory inputs to the olivary nucleus are gated so that the CF fires only at specific times<sup>40</sup>, resulting in a frequency of about 1 Hz *in vivo*<sup>38</sup>. Llinás has proposed that the olivocerebellar circuit serves as a clock that is essential for the proper timing of movements<sup>41</sup>. None of these authors has attributed any functional role to cerebellar LTD (Refs 9 and 41).

Probably the most serious problem for the MAIT is the required relative timing of the CF and PF inputs that is necessary to induce LTD. In all published experiments *in vivo*<sup>42–44</sup> and in slice<sup>8,45</sup>, the CF input is applied before or together with the PF input. Experiments that tested the relative timing show that maximal depression is attained if the CF input occurs 10 ms to 100 ms before the PF (Refs 44 and 46), so that the rise in the concentration of  $\text{Ca}^{2+}$  that is caused by the CS (Refs 47 and 48) is maximal at the time of activation of PFs. However, such a sequence is opposite to what classical conditioning and the MAIT would suggest, as the error signal that is carried by the CF should come after the sensory input (using activation of the PF as the conditioned stimulus).

Finally, the central assumption of MAIT, that is, the dependence of LTD on CF activation, must be questioned. Experiments with slice preparations<sup>8,45,49</sup> and cell cultures<sup>50,51</sup> have not only confirmed the existence of LTD but have also provided insights into the pharmacological and biochemical properties of

LTD (for review, see Ref. 2). Long-term depression in P-cells can be induced by activation of AMPA and metabotropic glutamate receptors<sup>51,52</sup> in conjunction with an increased dendritic concentration of  $\text{Ca}^{2+}$  (Refs 45 and 53). According to the MAIT, release of glutamate by the PF activates the AMPA and metabotropic glutamate receptors, while the CF input causes influx of  $\text{Ca}^{2+}$  through voltage-gated dendritic  $\text{Ca}^{2+}$  channels<sup>47,48</sup>. However, several groups have shown, in the slice preparation, that any mechanism that causes an increase in the concentration of  $\text{Ca}^{2+}$ , such as depolarization of the P-cell, will induce LTD of activated PF synapses<sup>45,49</sup>. These experiments show that activation of CFs is not necessary for induction of LTD *in vitro*, and that activation of PFs alone might be sufficient, providing that the concentration of  $\text{Ca}^{2+}$  is high enough at the same time.

Recently, high-resolution  $\text{Ca}^{2+}$  imaging of P-cells in slices has demonstrated that co-activation of a small number of PF synapses on the same dendritic region can open  $\text{Ca}^{2+}$  channels, causing localized and graded increases in the concentration of  $\text{Ca}^{2+}$  in spines and spiny dendrites<sup>54,55</sup>. On the basis of the existing experimental evidence<sup>45,49</sup>, I propose that such local increases in the concentration of  $\text{Ca}^{2+}$  are sufficient to induce LTD of the activated PF synapses. Parallel-fibre synapses should be able to induce their own depression because the increase in the concentration of  $\text{Ca}^{2+}$  coincides with the activation of AMPA and metabotropic glutamate receptors. This assumption contradicts evidence against PF-induced LTD from older experiments *in vivo*<sup>42,43</sup>. However, induction of LTD is not easy to achieve *in vivo*, as 100 to 1000 CF–PF pairings were required to induce LTD in P-cells<sup>42–44</sup> (this number of pairings in itself is difficult to reconcile with the MAIT). This contrasts with more recent studies that used slice preparations in which eight pairings were sufficient<sup>45</sup>. It seems that the experimental paradigm *in vivo* is not very sensitive, which explains why no PF-induced LTD was recorded.

Some of the differences between the results obtained from studies *in vivo* and *in vitro* can be explained by the absence of inhibition in the latter, either by pharmacological block<sup>8,49</sup>, or by cutting the axons of inhibitory interneurons<sup>45</sup>. It is more difficult to induce cerebellar LTD if inhibition is present<sup>8,43</sup>. Some authors have proposed that this is a result of a suppression of the plateau potential that can follow a CS (Ref. 43), but such plateaus were often absent in experiments where LTD induction was achieved<sup>8</sup>. Recent  $\text{Ca}^{2+}$ -imaging experiments suggest that inhibition can suppress the influx of  $\text{Ca}^{2+}$  selectively during a CS (Ref. 56). The interference of inhibition with the induction of LTD has been used to explain experiments in which LTD could not be observed when MAIT predicted that it should be present<sup>7</sup>.

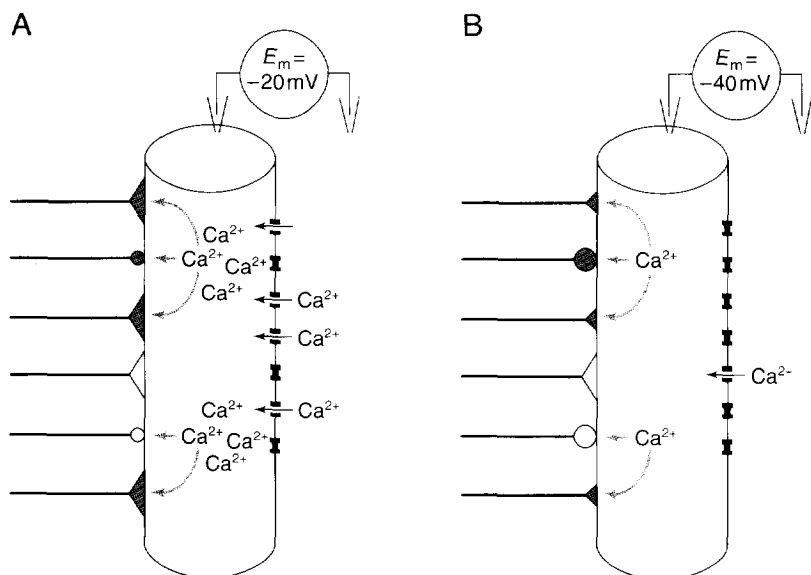
The MAIT do not explain why normal levels of inhibition in the cerebellar cortex can prevent the induction of LTD, while the interaction between inhibition and LTD is an essential part of the new hypothesis on the role of LTD that is presented here. It has been proposed recently that inhibition in the molecular layer has an important role in shaping the P-cell SS-firing pattern *in vivo*<sup>57</sup>. P-cells are well known for their typical burst firing in slice recordings, either

spontaneously or during injection of current<sup>58,59</sup>. This is caused by large dendritic  $\text{Ca}^{2+}$  spikes that are absent *in vivo*. In fact, P-cells fire only simple somatic spikes *in vivo*, except during the CS that is caused only by a CF input<sup>60,61</sup>. Simulations with a large, detailed computer model of the P-cell<sup>59</sup> have shown that the irregular SS-firing pattern *in vivo*<sup>60,62</sup> implies the absence of  $\text{Ca}^{2+}$  spikes that are large enough to invade the smooth dendrites, and that continuous inhibition is essential to suppress such  $\text{Ca}^{2+}$  spikes<sup>57</sup>. Without inhibition, the large number of PF inputs<sup>63</sup>, and the low activation threshold of the dendritic P-type  $\text{Ca}^{2+}$  channels<sup>64,65</sup>, will cause the P-cell model to burst continuously. These predictions have been confirmed with intracellular recordings from P-cells *in vivo*<sup>66</sup>. Local application of the GABA-receptor antagonist bicuculline caused P-cells to change their somatic firing pattern from an irregular SS firing to a regular bursting rhythm, accompanied by large dendritic  $\text{Ca}^{2+}$  spikes<sup>66</sup>.

If the assumption that it is important that P-cells maintain their typical SS-firing pattern *in vivo* is made, then a proper level of inhibition is crucial. However, the inhibitory circuitry onto P-cells is feedforward only and, therefore, is maladapted to regulate the level of inhibition. The inhibitory basket cells and stellate cells are excited only by PF axons and, except for the sparse Purkinje-axon collaterals<sup>5</sup>, there are no feedback connections between P-cells and the rest of the cerebellar cortex. The feedforward excitation and inhibition in the molecular layer of the cerebellum is in contrast with allo- and neocortex, where pyramidal cells receive massive feedback excitation and inhibition<sup>67</sup>. Instead, P-cells receive more than 150 000 excitatory PF inputs<sup>63</sup>, and individual inputs are so strong that co-activation of 50 PFs can drive the P-cell over the firing threshold<sup>68</sup>. Therefore, it is not difficult to imagine conditions in which the excitatory input onto an individual P-cell would saturate, causing it to fire dendritic  $\text{Ca}^{2+}$  spikes<sup>57</sup>. It seems unlikely that no mechanisms are present to normalize the excitation, and prevent overstimulation by increasing the inhibitory input, reducing the excitatory drive, or both. One such mechanism could be a downregulation of dendritic  $\text{Ca}^{2+}$  channels<sup>69</sup> but this seems unlikely as suppression of inhibition causes P-cells to burst *in vivo*<sup>66</sup>. Also, the dendritic  $\text{Ca}^{2+}$  channels might have other important functions that do not necessitate large dendritic spikes, such as amplifying PF inputs *in vivo*<sup>65,70</sup>.

I propose that PF-induced LTD is a mechanism that provides the missing local negative feedback. This hypothesis assumes that patterns of PF inputs that overexcite part of a dendrite cause LTD of the activated synapses. This depression involves only a small fraction of the activated synapses, consisting of the PF synapses on excessively depolarized regions. In large parts of the dendrite, local inhibition is strong enough to balance the PF input, and no plasticity is induced. Consequently, it is difficult to measure PF-induced LTD unless the response to localized PF inputs is recorded.

The hypothesis is shown in more detail in Fig. 1. In this example, inhibition is weak initially, and a strong PF input causes a large depolarization of the part of the dendrite shown (Fig. 1A). This depolarization opens voltage-gated  $\text{Ca}^{2+}$  channels, and the



**Fig. 1. Long-term depression (LTD) and potentiation of inhibitory inputs as a local negative feedback process.** A small part of a Purkinje-cell (P-cell) dendrite is shown. Parallel-fibre (PF) synapses are represented by triangles, and inhibitory synapses are represented by circles. Size corresponds to synaptic strength, and shaded synapses are active. **(A)** Before LTD. The dendrite is being overstimulated by the co-activation of several PF inputs. This results in a depolarization and influx of  $\text{Ca}^{2+}$ . Repeated increases in the concentration of  $\text{Ca}^{2+}$  will induce LTD of the active PF synapses, and potentiation of all inhibitory synapses, resulting in the situation shown in **B**. After LTD. Now, co-activation of the same, depressed PF synapses, combined with the potentiated inhibitory inputs, causes a much smaller depolarization and only a small increase in the concentration of  $\text{Ca}^{2+}$  that is insufficient to induce any additional changes in synaptic strength.

local concentration of  $\text{Ca}^{2+}$  increases every time the PF inputs are active. If the concentration of  $\text{Ca}^{2+}$  crosses a certain (unknown) threshold repeatedly, LTD of the active PF inputs is induced. This results in a net reduction of the excitatory drive on that part of the P-cell dendrite, keeping the concentration of  $\text{Ca}^{2+}$  within acceptable ranges (Fig. 1B). The efficacy of the PF depression is increased by a potentiation of the inhibitory inputs that is also elicited by the increased concentration of  $\text{Ca}^{2+}$ . Plasticity of the inhibitory synapses on P-cells has been reported recently<sup>71–73</sup>.  $\gamma$ -Aminobutyric acid receptor-mediated  $\text{Cl}^-$  currents are potentiated after short trains of activation of CFs (Ref. 72) or after any other cause of increased dendritic concentrations of  $\text{Ca}^{2+}$  (Refs 71–73).

In summary, this hypothesis proposes that LTD and plasticity of inhibitory inputs is used to balance the respective strengths of excitatory and inhibitory inputs on P-cells correctly. It explains why it is more difficult to induce LTD when normal inhibition is present, and why inhibitory inputs undergo an opposite form of plasticity. Moreover, it becomes evident why PF synapses do not undergo LTP when the concentration of  $\text{Ca}^{2+}$  increases even more, as is the case with excitatory inputs on many other neurones<sup>10</sup>.

The hypothesis can be taken one step further by also attributing a role to the potentiation of PF synapses as has been described by several authors<sup>8,46,49,50</sup>. Low-frequency stimulation of PFs without activation of CFs can induce a rapidly decaying potentiation of PF synapses, similar to the short-term potentiation (STP) of excitatory synapses that is described in the hippocampus<sup>74</sup>. Short-term potentiation of PF synapses seems to occur when no influx of  $\text{Ca}^{2+}$  is elicited, as it is easier to induce in hyperpolarized P-cells<sup>49</sup>. Short-term potentiation of PF

synapses could be used by P-cells to overcome inhibition that is too strong. However, it has not been demonstrated that STP can be induced when a normal level of inhibition is present.

The extinction of LTD seems to be variable. In most experiments, it persists for several hours<sup>2</sup> but in some cells it recovers after 40 min<sup>8,49</sup>. The longer persistence of LTD compared with STP of PF synapses suggests that preventing overstimulation is more important in this system that has the largest convergence of excitatory inputs in the mammalian brain<sup>5,63</sup>.

It is not possible to predict how often cerebellar LTD will be induced *in vivo*, because the detailed induction and extinction kinetics and the minimal concentration of  $\text{Ca}^{2+}$  that is required for induction of cerebellar LTD are not known<sup>2</sup>. It might be that PF-induced LTD is a gradual process, meaning that the change in synaptic gain is correlated with the concentration of  $\text{Ca}^{2+}$  beyond a certain threshold, and that extinction is relatively fast. If this is the case, LTD could be part of a dynamic equilibrium of synaptic strengths that adapts continuously and slowly to changes in excitation patterns. In the opposite case, where synapses would depress to a low, fixed level with little extinction, PF-induced LTD is expected to occur mainly during early life, until inputs are normalized sufficiently. In this context, it is interesting to note that investigations of LTD are usually performed on P-cells from fetal<sup>51</sup> or juvenile<sup>45,49</sup> animals.

Finally, this hypothesis does not propose any function for CF-induced LTD. On the basis of the arguments presented earlier, it could be suggested that CF-induced LTD does not occur under normal conditions *in vivo* because too many co-activations with the same PF inputs are required<sup>42–44</sup>. However, at this time, not enough is known about the quantitative requirements for the induction of any form of cerebellar LTD. To further clarify this issue, and to provide experimental proof of this hypothesis, more-detailed studies of the induction of LTD in slice preparations are required. The numbers of CF-PF co-activations that are required for CF-induced LTD, and the number of PF activations that are required for PF-induced LTD should be measured experimentally. We need to know if induction of LTD is a threshold process and, in addition, the critical dendritic concentrations of  $\text{Ca}^{2+}$  should be determined. A quantitative study of extinction of LTD, and its relationship to the induction procedures that are used would also be useful. However, the hypothesis that is presented here can only be (dis)proved by combined *in vivo* and *in vitro* experiments. A prediction of this hypothesis is that LTD will be induced more frequently if inhibition of the P-cells is suppressed, and less frequently if inhibition is potentiated. Syringes could be implanted to block or increase inhibition in the cerebellum chronically at one side, the animal could be killed, and the strengths of PF synapses from the left and right side of the cerebellum could be compared. The strength of single PF synapses can be measured in P-cells in the slice preparation by stimulation of individual granule cells<sup>68</sup>, but many measurements would be required because of the large variability of the amplitude of responses to activation of PF synapses<sup>68</sup>. A

similar procedure could be used to explore whether CF-induced LTD occurs *in vivo*. This would require one-sided lesions of the olivary nucleus.

This hypothesis proposes that LTD is part of a local regulatory mechanism that is required for the normal function of P-cells. An implicit assumption is that locally controlled changes in the gain of PF synapses do not interfere with the function of the cerebellar cortex. This is in contrast to the MAIT where PF synaptic strengths encode learned information. If motor learning is not the function of P-cells and the cerebellum, then what could it be? Recent experimental evidence suggests that the human cerebellum might be involved in cognitive and language functions<sup>75</sup>. Bower has suggested that the fractured spatial<sup>76</sup> and complex temporal<sup>77</sup> properties of the MF inputs provide important clues to cerebellar function<sup>76</sup>. On the basis of these results, and on my own modelling work<sup>57,78</sup>, Bower and I have proposed that the P-cell can operate as a filter that is responsive to fast variations in PF input activity, while slower changes in the frequency of PF firing are cancelled by the feedforward inhibition<sup>79</sup>. If P-cells indeed operate as temporal filters, they would be much less sensitive to the synaptic strength of PF inputs.

In conclusion, plasticity of synapses on P-cells might not be involved in motor learning at all, but instead might provide a local feedback mechanism that normalizes the total excitation of the P-cell at a level of depolarization where the simple SS rhythm is responsive maximally to changes in PF inputs, and where no large Ca<sup>2+</sup> spikes are generated. This feedback process is initiated by localized elevations of the dendritic concentration of Ca<sup>2+</sup>, which is an indicator of the level of depolarization caused by the synaptic input.

### Selected references

- 1 Hebb, D.O. (1949) *The Organization of Behavior: a Neuro-psychological Theory*, John Wiley
- 2 Linden, D.J. (1994) *Neuron* 12, 457–472
- 3 Marr, D.A. (1969) *J. Physiol.* 202, 437–470
- 4 Albus, J.S. (1971) *Math. Biosci.* 10, 25–61
- 5 Ito, M. (1984) *The Cerebellum and Neural Control*, Raven Press
- 6 Llinás, R., Yarom, Y. and Sugimori, M. (1981) *Fed. Proc.* 40, 2240–2245
- 7 Ito, M. (1989) *Annu. Rev. Neurosci.* 12, 85–102
- 8 Sakurai, M. (1987) *J. Physiol.* 394, 463–480
- 9 Bloedel, J.R. (1992) *Behav. Brain Sci.* 15, 666–678
- 10 Artola, A. and Singer, W. (1993) *Trends Neurosci.* 16, 480–487
- 11 Farrant, M. and Cull-Candy, S.G. (1991) *Proc. R. Soc. London Ser. B* 244, 179–184
- 12 Llano, I. *et al.* (1991) *J. Physiol.* 434, 183–213
- 13 Hardiman, M. J. and Yeo, C.H. (1992) *Eur. J. Neurosci.* 4, 966–980
- 14 Krupa, D.J., Thompson, J.K. and Thompson, R.F. (1993) *Science* 260, 989–991
- 15 Harvey, J.A. *et al.* (1993) *J. Neurosci.* 13, 1624–1635
- 16 Perrett, S.P., Ruiz, B.P. and Mauk, M.D. (1993) *J. Neurosci.* 13, 1708–1718
- 17 Hesslow, G. (1994) *J. Physiol.* 476, 245–256
- 18 Aiba, A. *et al.* (1994) *Cell* 79, 377–388
- 19 Conquet, F. *et al.* (1994) *Nature* 372, 237–243
- 20 Nakanishi, S. (1992) *Science* 258, 597–603
- 21 Aiba, A. *et al.* (1994) *Cell* 79, 365–375
- 22 Holmes, G. (1917) *Brain* 40, 461–535
- 23 Ito, M. (1982) *Annu. Rev. Neurosci.* 5, 275–298
- 24 Ghelarducci, B., Ito, M. and Yagi, N. (1975) *Brain Res.* 87, 66–72
- 25 Watanabe, E. (1984) *Brain Res.* 297, 169–174
- 26 Miles, F.A., Braitman, D.J. and Dow, B.M. (1980) *J. Neurophysiol.* 43, 1477–1493
- 27 Miles, F.A. and Lisberger, S.G. (1981) *Annu. Rev. Neurosci.* 4, 273–299
- 28 Lisberger, S.G. *et al.* (1994) *J. Neurophysiol.* 72, 954–973
- 29 Lisberger, S.G. (1994) *J. Neurophysiol.* 72, 974–998
- 30 Andersson, G. and Armstrong, D.M. (1987) *J. Physiol.* 385, 107–134
- 31 Lou, J.S. and Bloedel, J.R. (1992) *J. Neurophysiol.* 68, 1820–1833
- 32 Yanagihara, D. and Udo, M. (1994) *Neurosci. Res.* 19, 245–248
- 33 Ebner, T.J., Yu, Q.-X. and Bloedel, J.R. (1983) *J. Neurophysiol.* 50, 205–219
- 34 Sato, Y. *et al.* (1992) *J. Neurophysiol.* 68, 2051–2062
- 35 Ojakangas, C.L. and Ebner, T.J. (1992) *J. Neurophysiol.* 68, 2222–2236
- 36 Dugas, C. and Smith, A.M. (1992) *J. Neurophysiol.* 67, 483–495
- 37 Voogd, J. and Bigare, F. (1980) in *The Inferior Olivary Nucleus: Anatomy and Physiology* (Courville, J., de Montigny, C. and Lamarre, Y., eds), pp. 207–235, Raven Press
- 38 Sasaki, K., Bower, J.M. and Llinás, R.R. (1989) *Eur. J. Neurosci.* 1, 572–586
- 39 Llinás, R.R. and Yarom, Y. (1981) *J. Physiol.* 315, 549–567
- 40 Lampl, I. and Yarom, Y. (1993) *J. Neurophysiol.* 70, 2181–2186
- 41 Welsh, J.P. (1995) *Nature* 374, 453–457
- 42 Ito, M., Sakurai, M. and Tongroach, P. (1982) *J. Physiol.* 324, 133–134
- 43 Ekerot, C.-F. and Kano, M. (1985) *Brain Res.* 342, 357–360
- 44 Ekerot, C.-F. and Kano, M. (1989) *Neurosci. Res.* 6, 264–268
- 45 Konnerth, A., Dreessen, J. and Augustine, G.J. (1992) *Proc. Natl Acad. Sci. USA* 89, 7051–7055
- 46 Schreurs, B.G. and Alkon, D.L. (1993) *Brain Res.* 631, 235–240
- 47 Knöpfel, T., Audinat, E. and Gähwiler, B.H. (1991) *Eur. J. Neurosci.* 3, 343–348
- 48 Miyakawa, H. *et al.* (1992) *J. Neurophysiol.* 68, 1178–1189
- 49 Crepel, F. and Jaillard, D. (1991) *J. Physiol.* 432, 123–141
- 50 Hirano, T. (1990) *Neurosci. Lett.* 119, 141–144
- 51 Linden, D.J. *et al.* (1991) *Neuron* 7, 81–89
- 52 Ito, M. and Karachot, L. (1990) *Neurosci. Res.* 8, 303–307
- 53 Sakurai, M. (1990) *Proc. Natl Acad. Sci. USA* 87, 3383–3385
- 54 Midtgaard, J., Lasser-Ross, N. and Ross, W.N. (1993) *J. Neurophysiol.* 70, 2455–2469
- 55 Eilers, J., Augustine, G.J. and Konnerth, A. (1995) *Nature* 373, 155–158
- 56 Callaway, J.C., Lasser-Ross, N. and Ross, W.N. (1995) *J. Neurosci.* 15, 2777–2787
- 57 De Schutter, E. and Bower, J.M. (1994) *J. Neurophysiol.* 71, 401–419
- 58 Llinás, R.R. and Sugimori, M. (1980) *J. Physiol.* 305, 197–213
- 59 De Schutter, E. and Bower, J.M. (1994) *J. Neurophysiol.* 71, 375–400
- 60 Armstrong, D.M. and Rawson, J.A. (1979) *J. Physiol.* 289, 425–448
- 61 Montaloro, P.G., Palestini, M. and Strata, P. (1982) *J. Physiol.* 332, 187–202
- 62 Murphy, J.T. and Sabah, N.H. (1971) *Brain Res.* 25, 469–482
- 63 Harvey, R.J. and Napper, R.M.A. (1991) *Prog. Neurobiol.* 36, 437–463
- 64 Regan, L.J. (1991) *J. Neurosci.* 11, 2259–2269
- 65 Llinás, R.R. and Sugimori, M. (1992) in *The Cerebellum Revisited* (Llinás, R.R. and Sotelo, C., eds), pp. 167–181, Springer-Verlag
- 66 Jaeger, D. and Bower, J.M. (1994) *Exp. Brain Res.* 100, 200–214
- 67 Shepherd, G.M. (1990) *The Synaptic Organization of the Brain*, Oxford University Press
- 68 Barbour, B. (1993) *Neuron* 11, 759–769
- 69 Turrigiano, G., Abbott, L.F. and Marder, E. (1994) *Science* 264, 974–977
- 70 De Schutter, E. and Bower, J.M. (1994) *Proc. Natl Acad. Sci. USA* 91, 4736–4740
- 71 Llano, I., Leresche, N. and Marty, A. (1991) *Neuron* 6, 565–574
- 72 Kano, M. *et al.* (1992) *Nature* 356, 601–604
- 73 Vincent, P., Armstrong, C.M. and Marty, A. (1992) *J. Physiol.* 456, 453–471
- 74 Malenka, R.C. and Nicoll, R.A. (1993) *Trends Neurosci.* 16, 521–527
- 75 Leiner, H.C., Leiner, A.L. and Dow, R.S. (1993) *Trends Neurosci.* 16, 444–447
- 76 Bower, J.M. and Kassel, J. (1990) *J. Comp. Neurol.* 302, 768–778
- 77 Morissette, J. and Bower, J.M. (1991) *Soc. Neurosci. Abstr.* 17, 1383
- 78 De Schutter, E. (1994) *Prog. Brain Res.* 102, 417–431
- 79 De Schutter, E. and Bower, J.M. (1993) *Soc. Neurosci. Abstr.* 19, 1588

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