# Cerebellar long-term depression

In a recent article[1], De Schutter stresses the possible importance of a negative control of excitation of Purkinje cells (P-cells) by parallel fibres (PFs) through a permanent resetting of PF–P-cell synapses by homosynaptic long-term depression (LTD). In this scheme, LTD no longer requires co-activation of PFs and climbing fibres (CFs) to occur, as established by numerous studies *in vivo* and *in vitro* on cerebellar LTD (Ref. 2). Furthermore, De Schutter suggests that the resetting effect of LTD would be the main physiological role of this phenomenon, as opposed to current views on the role of LTD in motor learning[3]. Although this somehow provocative new vista on LTD is very interesting in several aspects, we would like to raise several points where we are not in complete agreement with De Schutter.

First, De Schutter takes for granted that there is no long-term potentiation (LTP) in the cerebellum, because there are no NMDA receptors on P-cells. However, both Sakurai[4] and our group have shown that LTP can be induced at PF–P-cell synapses, and we have also shown that this long-term increase in synaptic efficacy can occur when PFs are activated alone[5], that is, the situation where De Schutter assumes LTD to occur.

Second, the claim that activation of a small number of PFs is sufficient to induce LTD at PF–P-cell synapses (that is, independently of CF activation) bypasses the fact that no-one has ever published a demonstration that LTD could be induced at PF–P-cell synapses by repetitive activation of PFs alone, even when the stimulating strength is sufficient to induce a local increase in the concentration of $Ca^{2+}$ in dendritic branches and dendritic spines[6].

Third, De Schutter explains the observed difficulties in inducing LTD *in vivo* by an inhibition by stellate and basket cells of the $Ca^{2+}$ plateau associated with complex spikes (produced by CFs). It seems to us that this is an implicit recognition of the crucial role of CFs in LTD induction.

Finally, it is well established that both granule cells and olivary neurones have a spontaneous activity *in vivo*[7]. This background activity certainly leads to frequent co-activations of P-cells by PFs and CFs – the situation known to induce LTD. Thus, in addition to a possible role in motor learning, such spontaneously induced LTD might enable a recurrent resetting of the strength of PF–P-cell synapses, which otherwise would undergo LTP progressively over time.

In conclusion, although we agree that LTD can play a role theoretically in resetting the strength of PF–P-cell synapses, we do not agree with the mechanism postulated by De Schutter. The mechanism that we propose is in agreement with both available data on mechanisms of associative cerebellar LTD, and with the fact that the destruction of olivary neurones in behaving rats leads to a progressive and permanent increase in the firing frequency of simple spikes of P-cells[8].

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In a recent Viewpoint article[1], De Schutter casts doubt on the validity of the Marr–Albus–Ito theories (MAIT), which assume that long-term depression (LTD) in the cerebellum [that is, persistent reduction of transmission efficacy at parallel-fiber (PF) to Purkinje-cell (P-cell) synapses caused by co-stimulation of the PFs and climbing fibers (CFs)] is an essential mechanism of motor learning. I would like to defend the theories by responding to the following four points raised by the author.

First, De Schutter argues that 'the MAIT do not explain why normal levels of inhibition in the cerebellar cortex can prevent the induction of LTD'. In my view, the difficulty in reproducing LTD in slice preparations without the use of an antagonist for inhibition[2] is a problem not of the theory, but of the experimental conditions specific to these in *in vitro* preparations. Conditions *in vitro* differ from conditions *in vivo* in various aspects such as metabolic rates and impulse traffic, but I would like to point out one practical factor. Within a slice 0.4 mm thick cut perpendicularly to PFs (the usual preparation), PF stimulation will inevitably activate inhibitory basket and stellate cells not only indirectly but also directly[3], thus tending to induce an abnormally high level of inhibition that interferes with induction of LTD. Hence, an antagonist is used routinely in investigating LTD (Ref. 4). However, LTD can be induced in slices even in the absence of an antagonist with the use of burst-pattern trains of pulses for costimulation of PFs and CFs (Ref. 5), probably because the effect of CF–PF conjunction accumulates during train pulses whereas the inhibition is saturated.

Second, De Schutter refers to the recent finding that PF impulses alone effectively induce an increase in $Ca^{2+}$ concentration in peripheral P-cell dendrites[6], and suggests that PF stimulation alone induces LTD-like depression in PF–P-cell synapses. Recently, Hartell in our laboratory confirmed the occurrence of such increases in $Ca^{2+}$ concentration, which, under certain stimulus conditions, induced LTD-like depression[7]. This increase in $Ca^{2+}$ concentration occurs only when PF stimuli induce sufficiently large EPSPs (more than 8–9 mV in peak size in cells held at around –70 mV membrane potential), whereas no such threshold has been recognized for induction of conventional LTD. The CF-induced increase in $Ca^{2+}$ concentration decays with a much slower time course than that induced by PF, and hence $Ca^{2+}$ accumulates more effectively during repetitive stimulation of CFs than during that of PFs. I agree that, under certain conditions, PF stimulation alone can induce LTD-like depression, and I have no particular objection to De Schutter's hypothesis concerning a possible role of this PF-induced depression. However, I emphasize that his hypothesis does not conflict with the MAIT at all. The two forms of depression, occurring under different stimulus conditions, should have different functional implications.

Third, reasons for controversies regarding adaptation of the vestibulo–ocular reflex (VOR) have been given[8,9]. Encoding of retinal errors by simple spikes of flocculus P-cells is not in conflict with the MAIT as argued by De Schutter[1], because it can be explained by involvement of the flocculus in adaptation not only of VOR but also of optokinetic response, that is, a reflex eye movement driven by retinal errors[10]. Of crucial importance is a problem of regional sampling bias in the monkey flocculus[11], and this must be solved properly in close reference to the fine microzonal structure demonstrated for the monkey flocculus[12,13] before the validity of the theory is challenged.

Fourth, some misgivings were expressed concerning the efforts to relate LTD to motor learning using cerebellar-

lesioned animals or gene-knockout mice. A number of pharmacological reagents that block LTD are now available, and they provide a promising means for investigating roles of LTD. For example, we demonstrated that VOR adaptation is abolished without any change of ocular dynamics when hemoglobin, a nitric-oxide scavenger that blocks LTD in slices, is applied locally to the flocculus[14].

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# *Reply*

I appreciate the positive comments on the theory I presented in a recent article[1], but I disagree with the criticisms.

First, in response to Blond and Crépel, I do mention parallel-fibre (PF)-induced potentiation and attribute a specific role to it[1]. However, I prefer to call it short-term potentiation (STP) instead of long-term potentiation, and some of the arguments for this distinction were presented[1]. Another important difference between this STP and LTP in other brain structures is that STP is more easily obtained in hyperpolarized Purkinje cells (P-cells)[2].

Second, considering the number of PF–climbing-fibre (CF) co-activations required to induce long-term depression (LTD) *in vivo*[3], it seems unlikely that spontaneous CF activity would be sufficient to provide the normalization function that I described[1]. Moreover, the increase in P-cell-firing frequency after destruction of the olivary nucleus cannot be caused by the progressive absence of LTD, as similar changes are seen within a few seconds after cooling of the olivary nucleus[4]. A more probable cause is changes in other inputs to P-cells, elicited by the silencing of CF contacts onto inhibitory cortical neurones[5] and neurones of the deep cerebellar nuclei[6].

Both letters raise the issue of the suppression of LTD-induction by inhibition. Experimental evidence suggests that both CF- and PF-induced LTD are more difficult to obtain when normal levels of inhibition are present. This can be explained by the reduction in $Ca^{2+}$ inflow caused by inhibitory inputs[7]. It is unlikely that stimulation artifacts in the slice preparation are the sole cause of the inhibition. First, during on-beam stimulation (used to activate PF for the induction of LTD), no IPSPs are observed in intracellular recordings, while they are obvious during off-beam stimulation[8]. Second, and more importantly, whole-cell voltage-clamp recordings of P-cells in slice preparations show the presence of continuous spontaneous inhibitory inputs[9].

Both Hartell and another group (Augustine, G., pers. commun.) have shown that PF stimulation alone can induce LTD in slice preparations. This experimental confirmation of PF-induced LTD supports my theory[1] and is in complete contradiction to the central part of the Marr–Albus–Ito theories, that is, that the PF synaptic strength is the memory trace of a learning process with the CF as teacher. The need for strong PF inputs to obtain LTD-induction might be caused by the holding potential (–70 mV), which is much lower than dendritic membrane potentials recorded *in vivo*[10]. It would be more relevant to compare the number of stimulations required for PF-induced LTD with the number for CF-induced LTD.

The role of LTD in adaptation of the vestibulo–ocular reflex has been an ongoing controversy between Ito's[11] and Lisberger's[12] groups. It is beyond the scope of my response to continue this discussion, and I advise the reader to read the original papers. Similarly, the role of nitric oxide (NO) in the induction of cerebellar LTD is quite controversial[13], and any conclusion based on the use of NO scavengers should be considered tentative.

Finally, the role of cerebellar LTD in conditioned learning has been put in further doubt by a recent paper from Ito's group[14]. They confirm that the CF input has to precede the PF input to obtain CF-induced LTD and that a classical conditioning paradigm does not induce any LTD in the slice preparation.

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## CORRIGENDUM

In the Letter to the Editor by Joel C. Glover in the November issue of *TINS* (Vol. 18, pp. 486–487), reference 5 was incorrect. The correct reference is shown below. We apologise to the authors and to the readers for this error.

**5 Marin, F. and Puelles, L.** (1995) *Eur. J. Neurosci.* 7, 1714–1738