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Computational significance of the cellular mechanisms for synaptic plasticity in Purkinje cells

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Abstract: The data on the cellular mechanism of LTD that is presented in four target articles is synthesized into a new model of Purkinje cell plasticity. This model attempts to address credit assignment problems that are crucial in learning systems. Intracellular signal transduction mechanisms may provide the mechanism for a 3-factor learning rule and a trace mechanism. The latter may permit delayed information about motor error to modify the prior synaptic events that caused the error. This model may help to focus future cellular studies on issues that are particularly critical for a computationally viable concept of cerebellar plasticity. **[CREPEL et al.; HOUK et al.; KANO; LINDEN; VINCENT]**

The latest data on the cellular mechanisms for synaptic plasticity in the cerebellum are nicely summarized by four of the target articles in this BBS special issue **(CREPEL et al., KANO; LINDEN; VINCENT**). It is possible and desirable to formulate computational models of these data in a form that constitutes learning rules if one is to gain an insight into the means by which the cerebellum contributes to motor learning. Figure 9 of another target article (**HOUK et al.** sect. 3.1) attempts to do this, based on evidence that was previously available, but here we have attempted to improve upon this by incorporating the latest cellular data, as summarized in the above mentioned articles.

From a computational perspective, one of the more important issues that the cerebellar mechanism for synaptic plasticity must confront is the problem of proper credit assignment **(HOUK et al.)**. This refers to the difficulty of directing training signals to appropriate sites in the network and at appropriate moments in the training process, in order for learning to be truly adaptive (Houk & Barto 1992; Minsky 1963). Efficient credit assignment generally begins with a three-factor learning rule in which weight change depends on (1) a presynaptic factor that marks active (and therefore participating) synapses as being eligible for modification, (2) a postsynaptic factor that identifies neurons that have actively participated in controlling a behavior, and (3) a training factor that rewards or punishes the network on the basis of performance. Furthermore, efficient credit assignment requires more specialized training information than

merely global reward or punishment signals. Assuming that individual climbing fibers (CFs) transmit specialized training information, the different signals must then be directed to appropriate sites in the network. The zonal organization of CF input directs training information to specific functional modules in the cerebellar cortex, which should facilitate this structural part of the credit assignment problem. Finally, and of particular consequence to this commentary, one must address the temporal part of the credit assignment problem, which concerns the delivery of training information at appropriate times. Because of transmission lags and sluggish dynamics, information about erroneous performance is always delayed (typically by 100 msec or more) so that it follows the synaptic events that actually control the erroneous performance. CF signals detecting errors in performance need to modify those earlier synaptic events if learning is to be adaptive.

The intracellular signal transduction

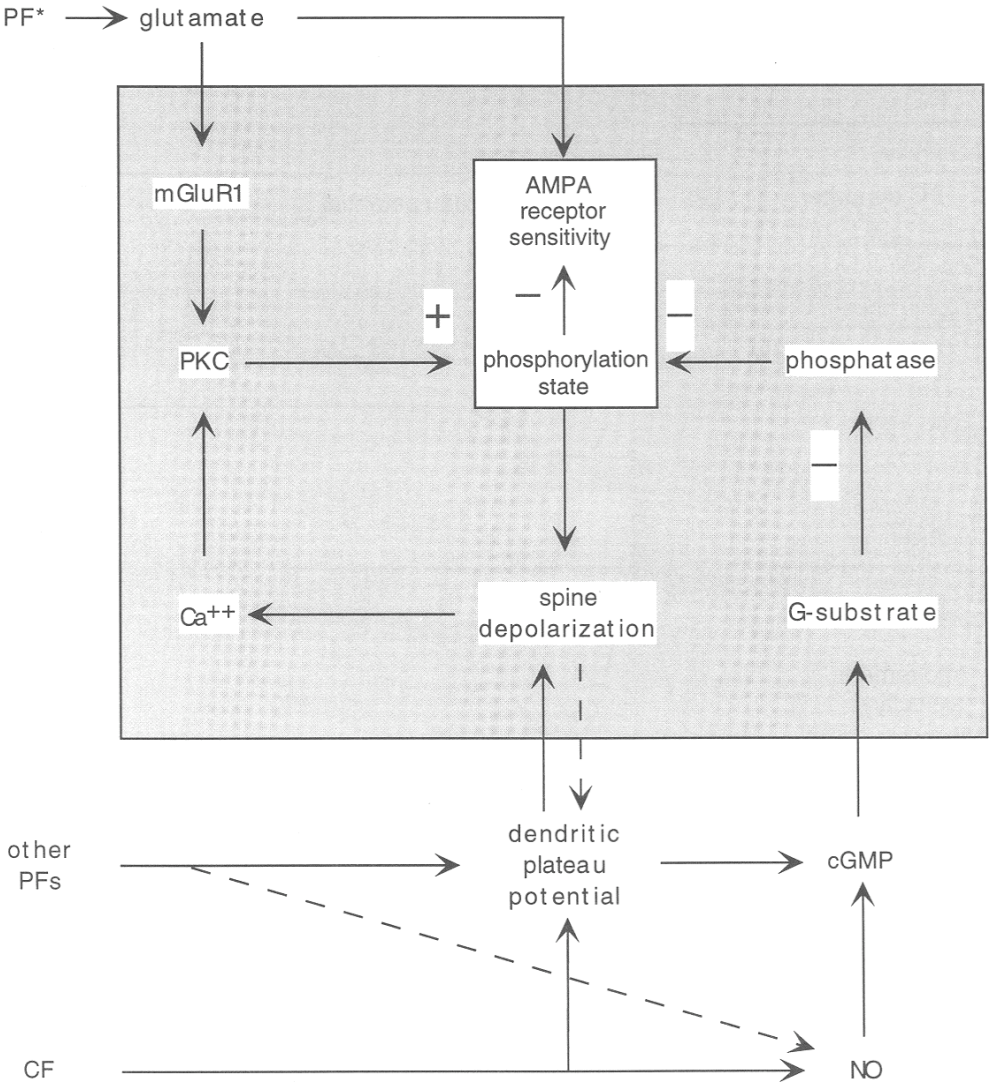

Figure 1 (Houk & Alford). Model of a 3-factor learning rule for cerebellar LTD. PF*, the parallel fiber input to an individual spine, is the presynaptic factor. PF* combines with cooperative inputs from many other PFs to produce a dendritic plateau potential, the postsynaptic factor in the learning rule. Training information conveyed by the CF input contributes the third factor in the proposed learning rule. The shaded box demarcates the borders of a synaptic spine. Abbreviations are defined in the text.

mechanisms that implement synaptic plasticity have properties that may be appropriate for mitigating some of these credit assignment problems (Houk & Barto 1992; Houk et al. 1995; Sutton & Barto 1981). The right side of Figure 1 summarizes the latest information about cerebellar intracellular signaling in a manner that emphasizes potential relationships to a three-factor learning rule and credit assignment. Those processes that are localized to individual spines are demarcated by a shaded box to emphasize the critical role of individual synapses in determining the computational competence of a learning rule. The AMPA receptor that mediates parallel fiber (PF) excitatory postsynaptic potentials (EPSPs) is the centerpoint of this model spine. Following the summary provided by **CREPEL et al.** (Fig. 6), the sensitivity of the AMPA receptor to glutamate neurotransmitter is regulated in a push-pull manner by the phosphorylation state of receptor protein. Phosphorylation is catalyzed by protein kinase C (PKC) and dephosphorylation is catalyzed by a local phosphatase. When the AMPA receptor is phosphorylated, it becomes less sensitive to glutamate, which is the cause of longterm depression (LTD) at PF synapses.

PKC needs to be activated before it can promote receptor phosphorylation, and this critical step appears to require both intracellular Ca^{++} and the activation of mGluR1 receptors by glutamate **(CREPEL et al.; LINDEN)**. Of these two cofactors, mGluRl receptor activation is likely to be the more specific and is thought to endow synapse specificity in the learning rule **(HOUK et al.; LINDEN)**. Although mGluR1 receptors are located in the postsynaptic membrane, they function as transducers of presynaptic activity in individual parallel fibers (PF* in Fig. 1). We therefore assume that mGluR1-mediated effects specify the presynaptic factor in the learning rule.

The second factor in the learning rule is postsynaptic activity. The glutamate released by the individual PF* will promote spine depolarization through its action on AMPA receptors; however, additional depolarization of the adjacent dendrite appears to be required to produce enough of the postsynaptic factor **(HOUK et al.)**. Figure 1 suggests that the combined depolarization caused by PF* plus cooperative inputs from many other PFs on the same dendrite produces a plateau potential which then facilitates spine depolarization. The latter would activate Ca^{++} channels in the spine, thus leading to the increase in spine Ca^{++} that is required as a cofactor in PKC activation (Fig. 1). From a computational standpoint, this contributes a dendrite-specific postsynaptic factor to the learning rule.

The third factor in the learning rule, the training information conveyed by CFs, needs to be directed to spines throughout the entire Purkinje cell and also to spines in adjacent cells that participate in the same cerebellar module. Furthermore, there must be some mechanism for overcoming the delayed nature of this training information. Figure 2 illustrates the hypothetical time course of local events in a spine in comparison with some of the global events that are important in the cerebellar control of movement.

The example in Figure 2 assumes that the subject makes a primary movement that undershoots the target position, followed by a secondary corrective movement. The upper trace shows the discharge frequency of a parallel fiber, PF*, that is responsive to the position of the limb. (The normal graded response of the PF is illustrated, as opposed to the synchronous volley that is used in most studies of LTD.) Assume further that the

increase in PF* firing contributes to the abrupt onset of a dendritic plateau potential in the Purkinje cell. Firing of this Purkinje cell then contributes to the inhibition that causes cerebellar nuclear discharge to abruptly fall off, as shown in the CBN trace. The CBN cells, and the motor cortical and rubral cells that they innervate, are the source of motor commands for voluntary movements of the limb (Houk et al. 1993). The abrupt termination of these CBN commands decelerates and, after some delay, terminates the primary movement. Since there is an error, a subsequent corrective movement, presumed to be mediated by an extracerebellar mechanism (cf. Berthier et al. 1993), moves the limb to the target.

Climbing fibers that are responsive to the proprioception of the movement are inhibited during the primary movement, thus preventing CF discharge **(HOUK et al.)**. However, these fibers appear to be responsive to corrective movements (Gilbert & Thach 1977), which is the postulated mechanism whereby a CF is able to signal the occurrences of errors in performance (Berthier et al. 1993). Note, however, the appreciable time delay T between the onset of the dendritic plateau potential that contributes to the premature termination of the primary movement and the CF signal that detects this error in performance. The delay between these events causes the temporal credit assignment problem discussed earlier.

Studies of cerebellar plasticity generally have not attempted to manipulate the relative timing of the experimental manipulations that are used to elicit LTD, and the poverty of such data has made it difficult to model temporal credit assignment. Recently, however, Chen and Thompson (1995) demonstrated that delaying CF activation by 250 msec after a PF volley facilitates the appearance of LTD, suggesting that there may be a cellular mechanism that compensates for T.

Another new finding that should be incorporated in the model learning rule is the involvement of nitric oxide (NO) in LTD, although the significance of this substance is still being debated **(CREPEL et al.; VINCENT)**. The model outlined in Figure 1 accepts the recent demonstration that the delivery of NO to the cytoplasm of Purkinje cells is a critical step in LTD (Lev-Ram et al. 1995). Furthermore, it couples this finding to the schema proposed in **CREPEL et al.** (Fig. 6) whereby NO activates cGMP and G-substrate which then inhibits the phosphatase that acts on AMPA receptors. The steps leading up to the formation of NO are less clear, but seem to be linked primarily to CF discharge with a lesser dependence (dashed arrow in Fig. 1) on PF activity (Shibuki & Okada 1991).

The features of the NO mechanism that seem most important from a computational standpoint are the following. (1) NO is highly defusible, which would allow a CF to exert its training influence on spines throughout the entire Purkinje cell it innervates as well as the spines of other Purkinje cells within the same module. This would provide appropriate structural credit assignment for a unified training action on an entire functional module. (2) NO has a very brief (~50 msec) period of action in Purkinje cells (Lev-Ram et al. 1995), which would limit the duration of its training influence to not more than the most recent corrective movement. (3) NO should act to stabilize prior phosphorylation of the AMPA receptor, which would allow the assignment of credit to those prior synaptic events that caused the original phosphorylation. We postulate that this stabilization mechanism could be a crucial factor in temporal credit assignment.
The proposed mechanism for temporal

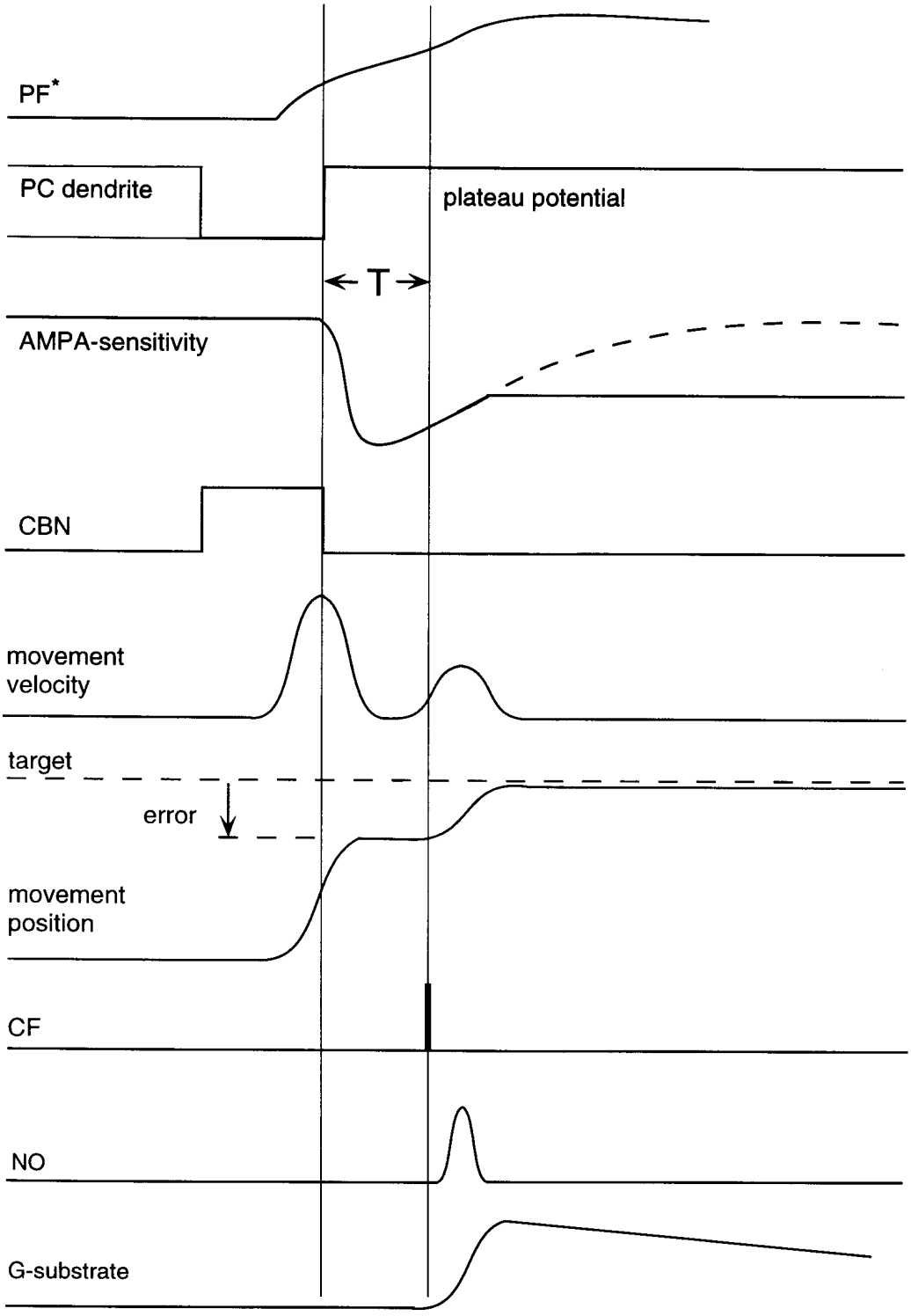

Figure 2. (Houk & Alford). Hypothetical time course of local and global events that are important in temporal credit assignment. T is the delay that must be overcome to achieve temporal credit assignment. The combination of PF* and the onset of the dendritic plateau potential produce the initial depression in AMPA-receptor sensitivity. The plateau potential also contributes to the abrupt cessation of CBN discharge, which terminates the motor command (prematurely in this case) that is sent to the neuromuscular system. The resultant undershooting error is detected due to the CF response to the corrective movement. NO release by CF input activates G-substrate to stabilize the depression in AMPA-receptor sensitivity, thus converting it into LTD. In this manner, these hypothetical events might resolve the temporal credit assignment problem.

credit assignment is further analyzed in the time plots of Figure 2. The production of the plateau potential in conjunction with PF input causes a reduction in the sensitivity of the AMPA receptors that is shortlived when ample phosphatase is available to dephosphorylate the receptor (dashed trace). However, if a movement error results in a CF spike, this leads to a brief expression of NO, followed by perhaps a longer expression of G-substrate. Since the latter inhibits the phosphatase, this interrupts the dephosphorylation of AMPA receptors, thus stabilizing their depression. In this manner, NO might function to convert a short-term depression into LTD. A key feature of this hypothesis is the relatively slow onset and long duration postulated for AMPA receptor phosphorylation. This time course spans the interval T required for proper temporal credit assignment.

In contrast with the input specificity of the above model, **KANO** reviews a mechanism for potentiation of inhibitory synapses that appears to lack input specificity. According to these findings, inhibitory GABAergic synapses made by basket cells onto Purkinje cells are potentiated if the basket cell fires while the Purkinje cell it innervates is depolarized. Any of the many PFs that excite this basket cell would subsequently have an enhanced inhibitory action. Although this mechanism lacks input specificity, it has output specificity, since inactive Purkinje cells, ones already inhibited by the firing basket cell, would not receive enhanced inhibition. It seems ideally suited for regulating the level of excitability in Purkinje cells. This could insure that properly assigned credit in the training of PF synapses would have as sensitive as possible an effect on Purkinje cell firing.

While there are many convergent findings regarding the mechanism of cerebellar LTD, some controversy clearly remains. It is likely that this represents, in part, redundancy within the protocols by which this process is elicited. In turn, the experimental demonstration of this redundancy may follow from the experimental paradigms used to induce LTD. Intense activation of a particular pathway may result in LTD when in the animal the pathway receives a less intense or an asynchronous input. It will be exciting to see, in the near future, the impact of timing of inputs to Purkinje neurons, and particularly whether this timing would be critical to the cascade of events that occur to initiate LTD when the animal is learning a motor task. Under these circumstances redundancy in the system may collapse to a necessary sequence of events, perhaps not unlike the model presented in this commentary.

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