

Current Concepts of Climbing Fiber Function

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This review examines several of the current postulates regarding the function of one of the most intriguing afferent systems in the brain, the climbing fiber system. The fact that these afferents are activated under a variety of conditions has contributed substantially to the diversity of postulates that have been proposed. In part because of the unique anatomical relationship between individual climbing fibers and the dendritic tree of Purkinje cells, these afferents have been proposed as a key input in establishing long-term plastic changes in the cerebellar cortex. This concept is contrasted with other postulates proposing that the heterosynaptic action of this system produces a short-lasting enhancement rather than a long-term depression of Purkinje cell responsiveness. Although a generally accepted view regarding climbing fiber function does not exist, this review emphasizes the extensive functional insights that have been reported and supports the notion that progress toward a complete understanding of these afferents will require an integration of their morphological characteristics with the fundamental physiological properties of their responses assessed in a variety of contexts and conditions. *Anat. Rec. (New Anat.)* 253:118–126, 1998. © 1998 Wiley-Liss, Inc.

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Cajal's elegant description of one of the most unique anatomical relationships in the brain, the extensive interface between the dendritic tree of a Purkinje cell and a single climbing fiber, triggered a century-long debate regarding the function of this unique afferent system. This relationship is illustrated in Figure 1, which also shows the organization of the other major input to these neurons, the mossy fiber–granule cell–parallel fiber projection. In general, the mossy fiber input is responsible for modulating the discharge of Purkinje cells in response to activity in descending pathways as well as to a wide variety of sensory inputs. In contrast, the climbing fiber input evokes a response which

is not graded and which occurs at a relatively low frequency.

From the onset of the electrophysiological studies characterizing the responses of Purkinje cells to these inputs, the responses evoked by these fibers were found to be as unique as their morphology. Primarily as a consequence of the classical experiments by Eccles, Llinas, and Sasaki (reviewed in 1), these afferents were shown to evoke a characteristic, large depolarization of Purkinje cells and an associated complex spike response that is distinctively different from the action potentials modulated by the other major afferent system to the Purkinje cell dendrites, the parallel fibers. An example of both the intracellularly and extracellularly recorded response of Purkinje cells to a climbing fiber input is shown in Figure 2. These responses were produced by stimulating the cerebellar white matter and consequently contain both an antidromically evoked action potential (the initial spike in both records evoked by stimulating the axon of the neuron in the cerebellar white matter) and the complex spike response evoked by the climbing fiber input. Based on their electrophysiological observa-

tions, Eccles and colleagues (for overview, see 1) formulated one of the first postulates regarding the functional action of this system, the read-out hypothesis. This view proposed that the depolarization evoked by the climbing fiber "read out" the level of excitability produced via the combined action of the mossy fiber–parallel fiber input directly to Purkinje cells and to the dendrites of the inhibitory interneurons. Although this postulate is no longer considered tenable, it focused the attention of physiologists on the unique role these fibers may play in regulating the output of the cerebellar cortex and more generally in regulating the functional properties of the cerebellum itself.

While not intended to be comprehensive, this review will provide an encapsulation of several theories of climbing fiber function that are relevant to current discussions regarding this system. Interestingly, none of these theories have been disproved, and all have at least some experimental support. Perhaps because critical questions remain unanswered, controversy still abounds on this topic, contributing to the fact that there are almost as many viewpoints on this topic as there are investigators in the field!

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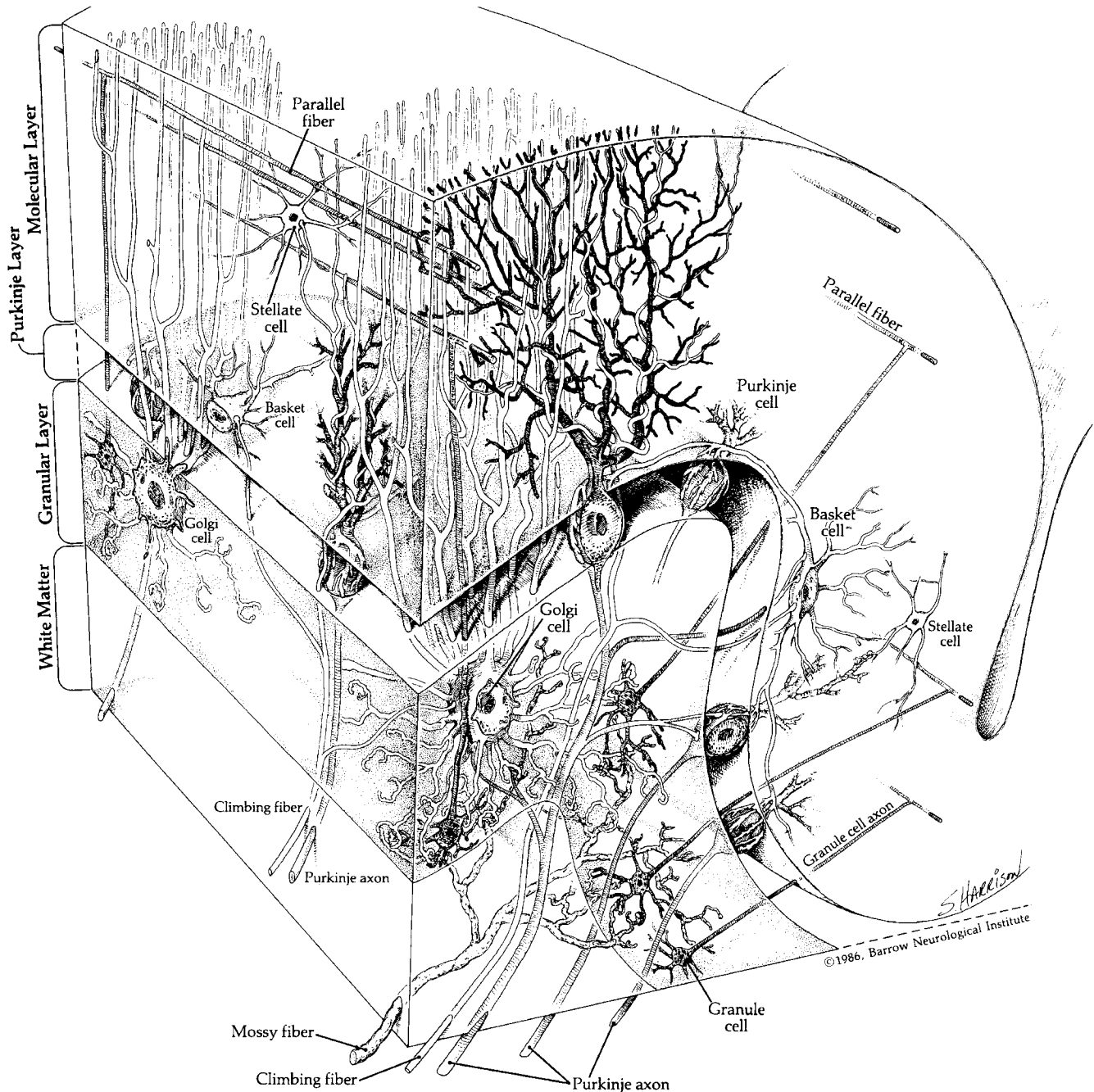


Figure 1. Illustration of the mammalian cerebellar cortex. A single folium is sectioned to reveal the planar organization of the Purkinje cell dendrites, the relationship of the climbing fiber to these structures, the interneurons (basket, Golgi, and stellate cells), and the mossy fiber system. (Reproduced from Bloedel²⁸ with permission of the publisher).

SPECIFIC VIEWS OF CLIMBING FIBER FUNCTION

Climbing Fibers as an Event or Error Signal

Several studies in unanesthetized decerebrate animals revealed that climbing fibers were capable of responding to very low intensity stimuli applied to their receptive field on the surface of

the body. These experiments as well as earlier electrophysiological studies characterizing the inputs to a variety of olivocerebellar projections² led to the proposal that the climbing fiber may be signaling the occurrence of an unexpected sensory stimulus during the course of a movement. This view was extended by postulating that these signals may represent error signals re-

flecting a discrepancy or mismatch between the intended and the actual movement. Other proponents of this concept argued that this sensory information is critical to the operation of the modules consisting of cerebellar cortical sagittal zones and the topographically organized output from related regions of the cerebellar nuclei.³

At least three lines of experimenta-

tion in awake behaving animals provide strong evidence supporting the view that the climbing fiber input can signal an unexpected interruption of intended and/or ongoing movement. First, Gellman et al.⁴ demonstrated that olivary neurons (neurons originating in the inferior olive) that were highly responsive to low intensity cutaneous stimuli applied passively were not activated when their receptive fields came in contact with the floor during ongoing locomotion. Second, in other experiments,⁵ climbing fibers were activated by a unique, unexpected perturbation. Cats were trained to walk on the rungs of a ladder. A rung was permitted to give way unexpectedly when contacted by the cat, producing a substantial deviation from the expected movement. Under this condition, climbing fiber inputs to Purkinje cells were activated. Third, experiments in our laboratory employed multiple single unit recordings from up to five sagittally oriented Purkinje cells in the intermediate cerebellar cortex to examine their responses when the forelimb of cats and ferrets ambulating encountered a bar intermittently placed in the trajectory of swing phase (reviewed in 6). These unexpected perturbations were very effective in evoking the synchronous activation of climbing fiber inputs to neighboring Purkinje cells within a sagittal zone.

The results of these studies indicate that climbing fibers can be activated in response to unexpected external stimuli encountered during movement as well as to low intensity passive stimuli applied to the body surface. Although this condition is an adequate one for activating these afferent fibers, other studies indicate that this is not the only condition under which climbing fibers respond during the performance of limb movements. For example, studies such as those performed in Mano's laboratory⁷ have shown that climbing fibers can be activated consistently during the execution of volitional, goal-directed movements in the absence of externally applied perturbations. However, even during these behaviors there is some indication that these afferents are responding to a mismatch between intended movement and the movement actually performed. For ex-

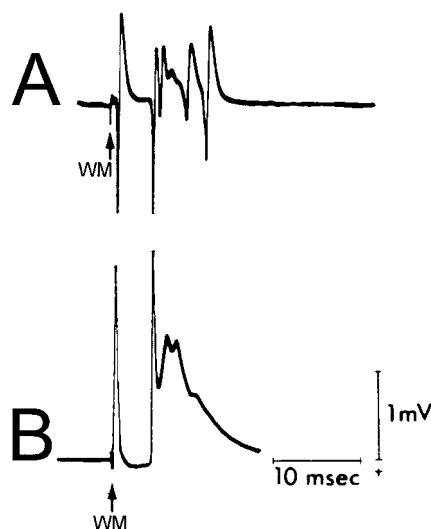


Figure 2. An extracellularly recorded (A) and intracellularly recorded (B) response evoked in two different Purkinje cells by a stimulus applied to the cerebellar white matter (WM).

ample, Ojakangas and Ebner⁸ observed that climbing fiber inputs to Purkinje cells were activated in trials in which a monkey made errors in moving a joystick to a target position after the relationship between the movement of the joystick and the movement of the cursor was changed. Together these data suggest that this general class of events, namely a mismatch between expected and unexpected behaviors or external stimuli, is one condition in which climbing fibers frequently are activated.

However, climbing fibers can be activated in the absence of any apparent unexpected event or mismatch during volitional movements, and, as will be discussed below, they may be capable of encoding specific aspects of a sensory stimulus rather than merely indicating the occurrence of a specific condition or event. Interestingly, even when specific features of sensory stimuli are encoded, their activation still may result from an error signal such as retinal slip (see the next section). Consequently, hypotheses based on error or event detection have substantial support in a wide variety of studies.

Climbing Fibers as Encoders of Sensory Information

Studies supporting the event hypothesis reviewed in the previous section

employed experimental conditions in which the animal encountered an unexpected sensory input whose characteristics were difficult to quantify or simply were not measured accurately as a systematic component of the protocol. Simpson and colleagues⁹ have obviated this problem by employing a paradigm in which a very specific, quantifiable sensory stimulus was employed, this being the movement of multiple spots of light across the retina in a specific direction. This visual input provides a directionally specific retinal slip signal which these investigators found to be very effective in activating climbing fiber inputs to specific locations within the cerebellar flocculus of the rabbit, a region having numerous interconnections with regions of the brainstem important in

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controlling eye movements. Functionally, these stimuli are comparable to the movement of images on the retina resulting from a discrepancy between the velocity of the eye movement actually performed and the movement required to hold the image stationary. An example of one of these experiments⁹ is shown in Figure 3. Spots of light are moved across the visual field in specific directions by rotating a sphere either clockwise (CW) or counterclockwise (CCW) on the horizontal axes indicated around the rabbit's head. The histograms at the end of each axis illustrate the responses to 15 rotations of the globe. As indicated in the key, the first half of the histogram displays responses to the CW rotation, and the second half to the CCW rota-

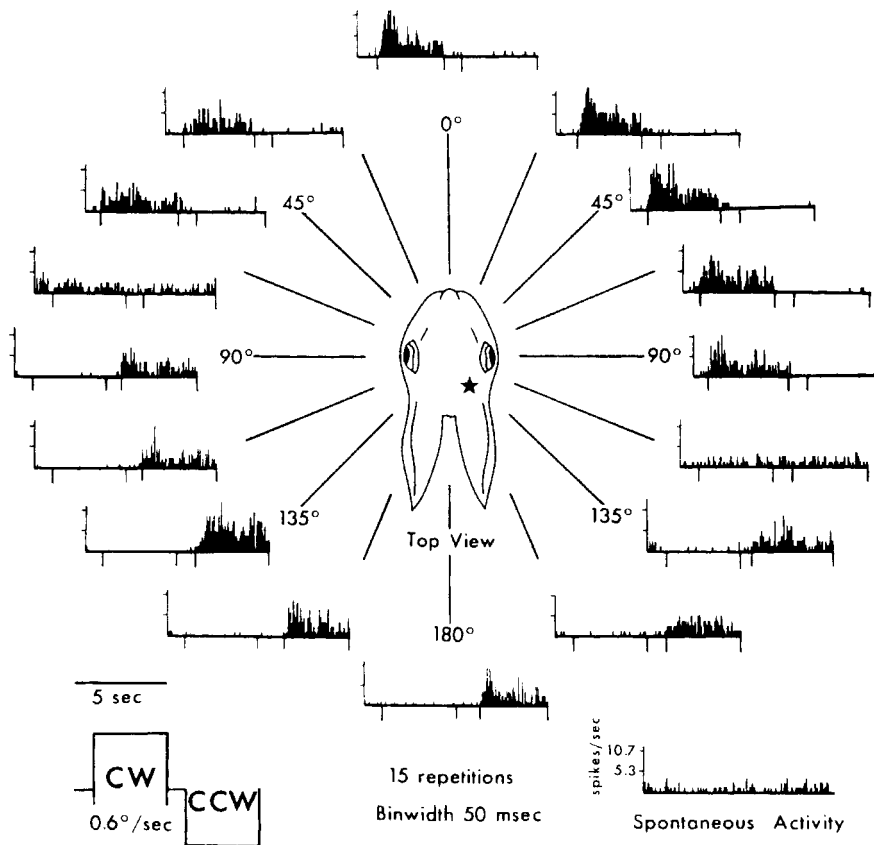


Figure 3. The response properties of complex spikes recorded in the rabbit flocculus in response to moving visual stimuli. (Reproduced from Leonard et al.⁹ with permission of the publisher).

tion. Notice that the magnitude of the response to either stimulus as well as its selectivity to the CW and CCW rotations is very dependent on the axis of rotation. These data provide evidence that the responses of a given climbing fiber input to a Purkinje cell can reflect a very specific feature of a sensory stimulus. However, as pointed out above, the stimuli themselves constitute a type of error signal, and consequently these data are quite consistent with the general concepts addressed in the previous section.

At present it is not known whether climbing fibers responding during limb movements also encode specific aspects of a sensory signal. For example, although a somatotopic organization of the climbing fiber input to the cerebellar cortex has been well established,¹⁰ the quantitative relationship between stimulus parameters and the activation of these afferents has not been examined systematically. Based on the extensive literature characterizing the responses of climbing fibers to

passive cutaneous stimuli, it certainly is feasible that some degree of encoding exists related to a specific aspect of the stimulus (e.g., direction) despite the all-or-nothing character of the Purkinje cell responses to brief cutaneous stimuli. Population encoding also may play a role. It also is possible that the spatial features of the receptive fields and their relationship on the body surface convey important information during the generation of limb movements.¹¹

Climbing Fibers as Regulators of Tonic Activity

Intriguing insights into a somewhat unique action of climbing fibers were generated by the laboratories of Strata and Batini (reviewed in reference 12). Their studies demonstrated that permanent or temporary lesions of the inferior olive produced clear modifications in the tonic or background discharge rate of Purkinje cells and their target neurons in the cerebellar nuclei.

In general, lesions of the olivocerebellar projection resulted in an enhanced discharge rate of Purkinje cells and an associated decrease in the spontaneous discharge rate of nuclear neurons. Interestingly, this effect is relatively immediate and could be produced shortly after reversibly suppressing the output of the inferior olive using a cooling probe.

The functional role of this tonic action of the climbing fiber system has not been fully elucidated. Subsequent studies of Strata's group demonstrated that the tonic effects of olivary cooling are correlated with a change in the dynamic characteristics of the vestibulo-ocular reflex (VOR), the reflex mediating conjugate eye movements in response to movement of the head. At the very least, this observation and the fact that a cerebellar syndrome can be produced by chronic olivary lesions¹³ indicate that the climbing

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fiber system is critical for the normal function of the cerebellum even though the afferent system responsible for modulating the simple spike activity of Purkinje cells, the mossy fiber system, is intact. These profound functional effects produced by reversible and irreversible olivary lesions could be due to a disruption of the heterosynaptic actions of the climbing fibers, which will be discussed more extensively below.

Climbing Fibers in the Generation of Complex Motor Sequences

The concept that the climbing fiber system can participate directly in the generation of phasic movements and motor sequences is in part based on early studies showing that the administration of harmaline, a drug that

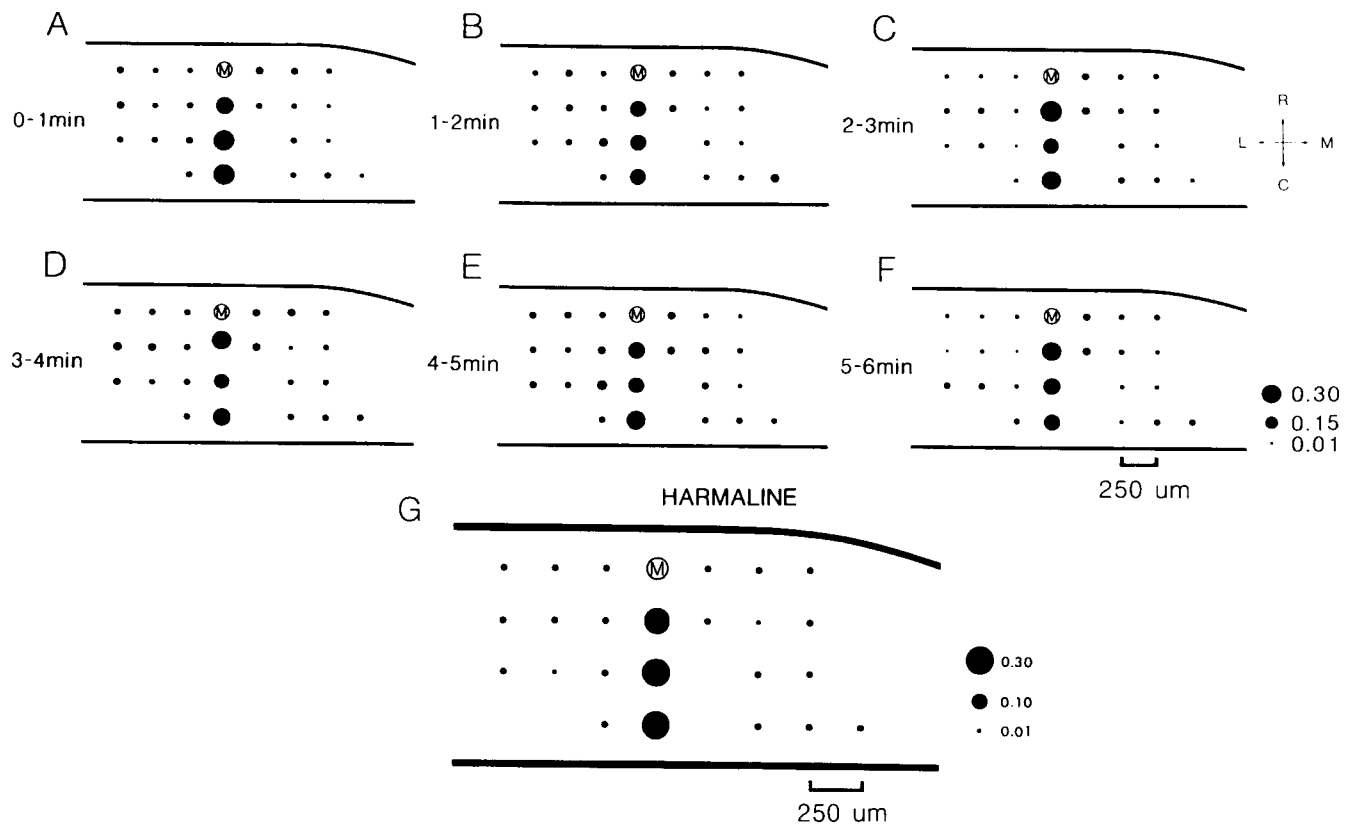


Figure 4. The distribution of correlated complex spike activity among 25 simultaneously recorded Purkinje cells, indicated as dots of varying sizes, aligned within several saggital zones. The diameter of the dot is proportional to the magnitude of correlation of discharge between cell M and other neurons. Recordings were obtained during successive 1 min epochs (A-F) and after the administration of harmaline (G). (Reproduced from Sasaki et al.¹⁴ with permission of the publisher.)

induces a synchronous rhythmic discharge among olivary neurons, produces phasic, tremor-like movements of the extremities. Furthermore, there was a high correlation between the rhythmic discharge of motor units and the complex spike responses of Purkinje cells. This fundamental property of the olivocerebellar system was pursued further by the laboratory of Llinas, who used multiple single unit recording techniques to demonstrate directly that Purkinje cells located within a sagittal zone exhibit highly correlated, synchronous activity.¹⁴ These effects are very clear in the experiment shown in Figure 4. In this experiment, the spontaneous discharge of 25 Purkinje cells was recorded over successive 1 min intervals, and the correlation in the discharge between cell M and the other neurons was measured and plotted (Fig. 4A-F). The magnitude of the correlations is indicated by the diameter of the circles representing the location of each cell. Notice the consistent correlation

among the complex spike responses of Purkinje cells oriented sagittally over the successive time intervals. The administration of harmaline (Fig. 4G) substantially enhanced the degree of correlation along the same sagittal band without disrupting the sagittal organization of the correlated neurons.

More recently, Llinás, Welsh, and collaborators¹⁵ discovered a high correlation between a naturally rhythmic movement, licking in the rat, and the complex spike discharge of Purkinje cells. Based on these findings and their previous studies of the olivocerebellar system, these authors proposed that the inferior olive contributes to the specification of the combinations of fundamental output units of the motor system required for the execution of complex movements and movement sequences. Thach and collaborators¹⁶ have challenged aspects of this view by reporting that the rhythmic behavior of complex spike discharges was not present in the discharge of

Purkinje cells recorded during a variety of motor behaviors in monkeys. Future studies undoubtedly will resolve this controversy.

The Heterosynaptic Action of Climbing Fibers

Perhaps the most interesting and widely discussed concepts of climbing fiber function are those pertaining to the action of these afferents on modulating the simple spike activity of Purkinje cells. An interest in this general issue appeared with the first discussions of climbing fiber function based on the properties of the inactivation response of Purkinje cells and the pause in simple spike activity that often follows it. The read-out hypothesis of Eccles and colleagues also was based on the effects of the climbing fiber on features of the responses evoked by the mossy fiber-parallel fiber system.

More recently, heterosynaptic effects of climbing fiber inputs have

been proposed as the basis for their action on the simple spike activity of Purkinje cells. The hypotheses based on these effects assume that these afferents are capable of inducing a change in the synaptic effectiveness of the parallel fiber input to Purkinje cell dendritic trees, resulting in a change in their responsiveness to inputs mediated by the mossy fiber–parallel fiber system. Two classes of heterosynaptic effects have been proposed: (1) a long-lasting change related to the establishment of memory traces in the cerebellar cortex and (2) a short-lasting change in the responsiveness or gain of the Purkinje cells to parallel fiber inputs.

Long-term heterosynaptic action of climbing fibers—long-term depression

Interest in the possibility that climbing fibers could induce a long-lasting, persistent change in Purkinje cell excitability through the action of climbing fibers was stimulated by the early theoretical work of David Marr in the late 1960s¹⁷ and led to the well-known Marr-Albus hypothesis. Marr proposed that, when climbing fibers activate the dendrites of Purkinje cells coincident with the arrival of parallel fiber inputs responding to behaviorally relevant inputs from the mossy fiber projections, a memory trace is established. Functionally, this interaction was proposed to reduce the responsiveness of Purkinje cells to the same subset of parallel fibers when these fibers were reactivated repeatedly during the learning of a movement. This reduction in responsiveness was believed to be persistent, representing the consequence of establishing an engram in the cerebellar cortex required for the retention and eventual recall of previously learned motor patterns.

This postulate was the basis for an extensive series of experiments performed by Ito and his colleagues.¹⁸ These investigators designed a paradigm, the conjunctive stimulation paradigm, which they felt implemented the conditions required to test adequately the provocative proposal of Marr. These studies demonstrated that the application of a stimulus activating the granule cell–parallel fiber input together with the climbing fiber

input to the same population of cells resulted in a long-lasting depression of Purkinje cell excitability, a phenomenon termed long-term depression or LTD.¹⁹ To further support this hypothesis, these same investigators demonstrated that the depression was selective for parallel fiber inputs that were activated during the application of the conjunctive stimuli. Following the establishment of LTD of Purkinje cells to the parallel fiber input activated during conjunctive stimulation, no comparable depression was found for the responses to parallel fibers that were not activated during the conjunctive stimulation paradigm. These observations established LTD as a potential mechanism for generating long-term plastic changes in the cerebellar cortex during the learning of motor tasks.

These observations led to detailed investigations into the cellular mecha-

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nisms responsible for LTD (reviewed in references 20,21). Although many interesting phenomena related to a variety of second messenger systems have been identified and described, the relationship of LTD to memory processes still is not clear. The fundamental studies on the cellular mechanisms underlying long-term depression certainly have provided strong evidence that associative processes, such as those occurring as a consequence of pairing conditioned and unconditioned stimuli in paradigms such as classical conditioning, are not necessary to produce this phenomenon. For example, it can be evoked by bathing the dendrites of the Purkinje cell in a slice preparation with putative excitatory transmitters that result in a massive depolarization of that cell. LTD even has been reported as a conse-

quence of stimulus paradigms restricted to the parallel fibers. These studies demonstrate that the action of the climbing fibers per se is not essential for LTD to occur.

The behavioral evidence supporting LTD in learning also is equivocal. Although initial reports by Gilbert and Thach²² argued that changes in complex and simple spike modulation occurred in a manner consistent with the Marr-Albus hypothesis, the more recent quantitative studies of Ojakanus and Ebner⁸ did not support this view. These investigators examined explicitly the changes in simple and complex spike modulation during the learning of goal-directed reaching movements requiring that the animal learn an altered relationship between the movement of a manipulandum and the movement of a cursor on a screen. In brief, the changes in the modulation of Purkinje cells were not found to be consistent with the Marr-Albus hypothesis. In another recent behavioral experiment, Schreurs and colleagues²³ demonstrated that LTD-related changes did not occur as a consequence of the classical conditioning of the eye-blink reflex in the rabbit. In fact, a persistent decrease in excitability (i.e., increased responsiveness) of Purkinje cells was noted within a specific sagittal zone in lobule HVI of the cerebellar cortex. Interestingly, although these findings fail to support a contribution of LTD to the classical conditioning of this reflex, they do support a long-lasting change in excitability of Purkinje cell dendrites associated with learning.

Recent studies employing genetic knockout techniques in mice have not been successful in providing uniform support for a causal link between LTD and the learning of specific tasks. A recent review by Llinas et al.²⁴ notes that studies employing this technique do not show parallel effects between the magnitude of changes in LTD and the extent of the learning assessed in the experiment. In summary, although available data provide initial evidence favoring the existence of long-term modifications in the excitability of Purkinje cells associated with learning a motor task, additional evidence will be required before LTD can be considered to play a fundamental role in acquisition and retention processes.

Short-term heterosynaptic action of climbing fibers

Our laboratory discovered that a spontaneous climbing fiber input not only evokes a pause in the simple spike activity but also may result in an increase or decrease in the discharge rate of Purkinje cells once its simple spike activity resumes (for review see Bloedel and Ebner²⁵). Furthermore, our laboratory demonstrated that the action of these afferents can modify the autocorrelation of the simple spike discharge after the pause.

Observing these changes in simple spike discharge rate following the pause suggested to Ebner and Bloedel that the climbing fiber input actually may be capable of modifying the short-term responsiveness of Purkinje cells to parallel fiber inputs. Based on this premise, we performed an extensive series of studies demonstrating that the modulation of simple spike responses evoked after the occurrence of the cell's climbing fiber input is enhanced and that this enhancement is short-lasting, decaying over a few hundred milliseconds at maximum. These changes in the responses were very unusual compared to effects that had been described previously, since they did not substantially change the profile of the response and could consist of an enhancement of both excitatory and inhibitory response components. An example of this effect is shown in Figure 5. The responses shown in these histograms were evoked by a natural cutaneous stimulus applied on the forelimb. Note that the response consisted of both an excitatory and an inhibitory response components. The simple spike responses first were sorted based on whether or not a complex spike was evoked by the stimulus. Next, the amplitude of both the excitatory and the inhibitory response components in the trials in which complex spikes were evoked (Fig. 5B) was calculated relative to the amplitude of the same components in the histogram constructed from trials in which no complex spikes were evoked by the stimulus (Fig. 5A). The fact that both R_E and R_I are greater than 100% indicates that the excitatory as well as the inhibitory response components were enhanced in those trials in which the climbing fiber input to the same cell

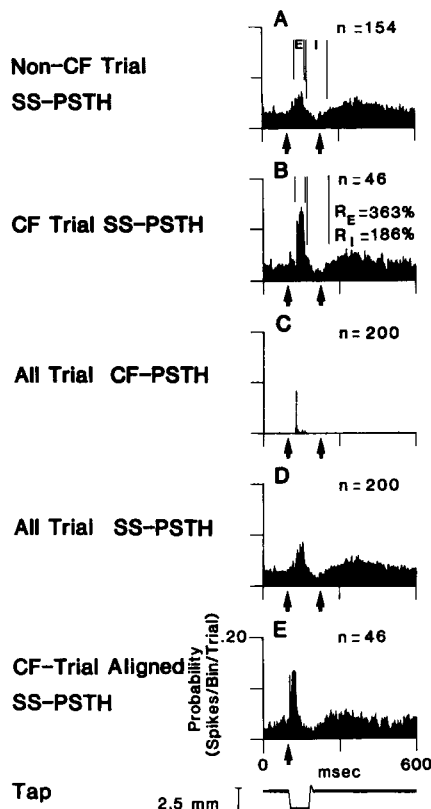


Figure 5. The effect of climbing fiber inputs on the simple spike activity of a Purkinje cell evoked by a natural cutaneous stimulus. A,B: Simple spike histograms constructed only from trials in which climbing fiber inputs were not or were evoked, respectively. C: Histogram of all the complex spike responses across all trials. D: Histogram of the simple spike responses across all trials. E: Simple spike responses aligned on the time of occurrence of the complex spikes in each trial in which they occurred. n, number of trials from which the indicated histogram is constructed; R_E , relative change in the amplitude of the excitatory response in trials in which the climbing fiber input occurred compared to the amplitude of the same response component in trials in which no climbing fiber inputs were evoked; R_I , relative change in the amplitude of the inhibitory response component in trials in which the climbing fiber input was evoked. Pairs of arrows along the x-axis indicate the response windows in which the response amplitudes were measured. (Reproduced from Bloedel and Kelly⁶ with permission of the publisher.)

was activated. The temporal relationship between the complex spike input and the simple spike response is shown in Figure 5E, a histogram constructed by aligning all trials on the occurrence of the complex spike rather than on the time at which the cutaneous stimulus was applied.

These data indicate that the charac-

teristics of this effect on the responsiveness of Purkinje cells are quite different than those of LTD. Rather than producing a long-term depression, a short-lasting enhancement of the simple spike responses was observed. These observations led to the “gain change” hypothesis, which proposed that the occurrence of climbing fiber inputs could produce a short-lasting increase in the gain of a Purkinje cell's response to its other primary input, the mossy fiber–parallel fiber projection. In order to address this concept in a more general framework, Bloedel and Kelly⁶ proposed the “dynamic selection” hypothesis. This viewpoint was intended to synthesize the specific observations on which the gain change hypothesis was based with the fundamental morphological and physiological organization of the climbing fiber and mossy fiber projections to the cerebellar cortex.

The features of this concept are illustrated in Figure 6. In addition to incorporating the gain change hypothesis, this view addresses an interesting and sometimes enigmatic feature of cerebellar organization. In brief, climbing fiber inputs from specific locations within the inferior olive are well organized in sagittal bands that are somatotopically organized. In contrast, although there is some banding of mossy fiber inputs, receptive fields representing a given region of the body tend to be distributed over multiple sites on the cerebellar cortical surface extending across different sagittal zones. As a consequence, it remains unclear how information pertinent to a given body region is processed via the mossy fiber system in a manner that implements the strict topographical organization of the cerebellar nuclei. This is important because this afferent projection is responsible for generating the graded modulation of Purkinje cell activity during the control of a variety of motor behaviors.

The distribution of activated mossy fiber and climbing fiber inputs is shown for three different conditions (Fig. 6) to illustrate how the dynamic selection hypothesis addresses this problem. It is assumed that a stimulus encountered by the paw activates the same distribution of mossy fiber inputs in each condition. However, because of the well-known convergence

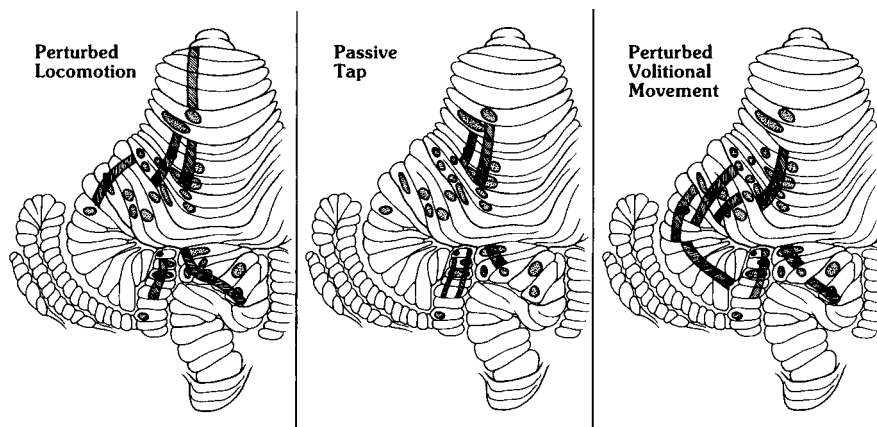


Figure 6. Explanation of the dynamic selection hypothesis. Oval-like patches on the cerebellum represent the distribution of mossy fiber inputs evoked by a stimulus applied to the same location on the paw under each of the three different functional conditions indicated above each panel. Stripe-like areas indicate the location of climbing fiber inputs activated under the same three conditions. (Reproduced from Bloedel and Kelly⁶ with permission of the publisher.)

of ascending and descending projections to the inferior olive, it also is assumed that a somewhat different distribution of climbing fiber inputs is activated in each, reflecting the specific behavioral conditions under which they are evoked. This condition-specific distribution of activated climbing fiber inputs in turn determines the location of those Purkinje cells most responsive to the ongoing modulation of their inputs from parallel fibers and inhibitory interneurons. This is depicted in Figure 6 as the differences in the regions of overlapping climbing and mossy fiber inputs under the three conditions. Given the strict topographical organization of the corticonuclear projection, this in turn would specify the organization of the output projections from the cerebellar nuclei that would be most highly modulated in relation to each behavior.

This view accounts for the fact that the climbing fibers can be activated in a number of functional contexts, and it provides one of the few postulates that integrates the topography of the corticonuclear projection, the receptive field distribution of mossy fiber inputs, and the organization of the olivocerebellar system with several functional properties of this projection. It also integrates the short-term heterosynaptic action of Purkinje cells with the tendency for these afferents to be activated synchronously in a sagittal distribution under specific behavioral conditions. However, like most current viewpoints, the dynamic

selection hypothesis should be regarded as a conceptual framework that undoubtedly will require modification as additional information regarding the climbing fiber system is acquired. It also must be acknowledged that the short-term enhancement described above has not been observed under all functional conditions. Nevertheless, short-term enhancement has been demonstrated in response to passive stimuli and in response to stimuli encountered during active movements, as reviewed above, and the possibility that the occurrence and even the relevance of these interactions may be task-dependent should not be overlooked.

CONCLUSIONS

To borrow a phrase commonly employed in Lake Wobegon, the "horse remains out of the barn" with regard to a generally accepted and well-substantiated viewpoint characterizing the precise function of the climbing fibers. Nevertheless, the spectrum of studies reviewed above provides a basis for optimism, since the data reveal important fundamental features of this system as well as critical interrelationships among a variety of experimental observations and even among the multiple concepts addressing the function of this system. In our view, these postulates and the findings on which they are based reveal the spectrum of relevant conditions in which climbing fibers are activated.

In general, these concepts fall into two categories: those related to the online processing of the cerebellar cortex and those pertaining to the establishment of long-term modifications in responsiveness relevant to the establishment of memory engrams. The data clearly indicate that the climbing fiber system is relevant to the online processing performed by the cerebellum. At present, the data implicating these afferents in the establishment of memory traces is yet not conclusive. The studies reviewed here strongly suggest that long-term changes in excitability can occur in Purkinje cells in association with learning. However, these changes were not consistent with a role for LTD, and the findings on this issue from the gene knockout experiments remain equivocal. It remains

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feasible that long-term changes related to learning occur in the cerebellum but that they are not established as a consequence of the climbing fibers' actions. In fact, the strongest data for learning-related plastic changes in the cerebellum implicate the target nuclei of the Purkinje cells (the vestibular and cerebellar nuclei) rather than the cerebellar cortex. Interestingly, the projections of the climbing fibers to the deep nuclei have been largely overlooked in most discussions regarding the function of these afferents.

It also should be emphasized that the occurrence of plastic changes of any type may be highly task-dependent, as emphasized by several of our recent studies.^{26,27} For example, block-

ing protein synthesis in the ipsilateral cerebellar interposed nuclei in the rabbit suppresses the acquisition of memory traces required for the retention of the classically conditioned eye-blink reflex. In contrast, cats can acquire complex, volitional forelimb movements while the ipsilateral dentate and interposed nuclei are inactivated by the injection of muscimol. Thus, although these data support the feasibility of plastic changes in the cerebellar nuclei related to eye-blink conditioning in the rabbit, they do not support a critical intracerebellar storage site related to the learning of the type of complex forelimb movements employed in our experiments.

In summary, we believe that a continued focus on integrating the fundamental morphological and functional properties of the climbing fibers in experiments using a variety of behavioral models will result in substantial progress in uncovering the elusive function of this intriguing system.

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