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Control of Cerebellar Nuclear Cells: A Direct Role for Complex Spikes?

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Abstract

The question of what modulates the firing of the cerebellar nuclei (CN) is one to which we presently have a surprisingly incomplete answer. Because most synaptic input to the CN originates from Purkinje cells (PCs), and simple spikes (SSs) are far more numerous than complex spikes (CSs), SSs are generally thought to be the dominant influence on the CN. However, evidence, reviewed here, suggests that this appears not to be the case in some physiologically important situations. As an alternative, we propose that CS activity may have at least as significant an effect on CN firing as do SSs. In particular, we suggest that CS activity has a role in controlling the bursts CN neurons show during various movements, during sleep states, and under ketamine–xylazine anesthesia. The ability to perform this role rests on the fact that CSs can be highly synchronized among PCs that project to the same CN neuron. Specifically, we suggest that synchronized CSs help determine the temporal course of the CN bursts, most often their offset, and that SSs and activity from cerebellar afferents may modulate the specific firing pattern within each burst. This joint control of CN activity may help explain anomalies present in the standard model for synaptic control of CN activity in which determination of CN firing patterns is attributed primarily to SSs.

Keywords

Synchrony; Olivocerebellar; Complex spike; Simple spike; Cerebellum; Purkinje cell

In trying to understand the cerebellum's role in motor coordination, and other functions, the question naturally arises of how its output to other brain regions is formed. A step toward answering this question is determining what modulates the activity of the cerebellar nuclei (CN), the major source of cerebellar efferents. In this paper, we discuss this issue, point out some problems with the standard view of CN control mechanisms, and suggest an alternative model, based on some recent investigations in our laboratory.

Are Simple Spikes the Dominant Modulator of CN Activity?

CN neurons are spontaneously active, typically firing at 30–50 Hz under in vitro conditions, because of their intrinsic membrane properties [1-7]. Superimposed on this intrinsic excitability is a seemingly straightforward pattern of synaptic connectivity primarily involving three sets of axons. Excitatory drive arrives mainly via two of these sets: collaterals of mossy fibers and of olivocerebellar axons; the third set comprises Purkinje cell

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(PC) axons, which are the major source of inhibitory synapses onto CN neurons. Of course, the mossy fiber and olivocerebellar axon collaterals could be further subdivided according to additional criteria, such as their origins, and even PC axons may not form a homogeneous class, as zebrin positive and negative PCs appear to generate complex spikes (CSs) that differ in wavelet number [8]. Nevertheless, for the present purposes, the basic tripartite division of the major synaptic sources seems sufficient. The remaining synapses in the CN mainly originate from intrinsic sources: local interneurons and collaterals of the CN projection cells; however, these latter synapses represent a relatively minor contribution percentagewise, and consistent with this fact, under in vitro conditions, application of synaptic blockers to CN slices produces little change in the spontaneous firing rates of CN neurons [6].

PC axonal terminals form, by far, the single largest class of synapses in the CN (~70%) [9, 10], suggesting that they should be the dominant synaptic influence over CN activity, an idea we will refer to as the “standard hypothesis”. The numerical superiority of PC axon terminals is compounded by their preferential location on the axon hillock, soma and proximal dendrites, where they comprise >95% of all terminals at these sites for large CN neurons in monkeys, and 78–86% of somatic synapses on rat CN neurons [11]. Moreover, the anatomical preponderance of PC terminals is reinforced by the disparity in the spontaneous firing rates of PC simple spikes (SSs, ~40–50 Hz) and the rates of at least the collaterals of olivocerebellar axons, as the latter typically fire at only ~1 Hz in behaving or anesthetized animals. Although a single parameter cannot fully describe the activity of mossy fiber collaterals given their diverse origin, evidence suggests that their firing rates are not so exceptional as to override the anatomical advantage of the PC axons. For example, pontine nuclear neurons, the single largest source of mossy fibers, display no spontaneous activity in vitro [12], and many have relatively low firing rates under anesthesia [13] and in awake animals [14]. Similarly, mossy fibers conveying ascending somatosensory information also show relatively low spontaneous rates compared with SS activity [15, 16]. However, mossy fibers can fire at high frequencies with appropriate stimuli or during specific behaviors [15-17].

Given the above facts, investigations into this issue have, not surprisingly, focused on the relationship between SS and CN activity. The inhibitory nature of PCs [18, 19], combined with their being the dominant synaptic input to CN neurons, suggests that an inverse relationship between SS and CN activity should exist. Such a relationship has indeed been found in certain circumstances. For example, stimulation of cerebellar afferent pathways evokes sequences of increases and decreases in CN firing, as well as increases in SS activity at latencies consistent with their causing the depressions in CN firing [20]. Moreover, cooling of the cerebellar cortex eliminates the inhibitory components of the CN responses [21].

The predicted inverse relationship between SSs and CN activity also appears to hold with regard to spontaneous activity. Cooling of the cortex sufficient to eliminate the activity of most PCs increases CN firing rates [21]. Conversely, lesions of the inferior olive (IO) cause a tonic increase in SS activity, and a corresponding decrease CN firing, both of which subside over time in a coordinated fashion [22-27]. Application of GABA-A antagonists to the cerebellar cortex increases SS activity [28, 29], and lowers CN firing rates (Blenkinsop and Lang, unpublished results). Thus, when considering either responses evoked by strong stimulation, or the basal level of activity over extended time periods, SS and CN activity appear to be inversely related, consistent with the standard idea of SS activity being the dominant modulator of CN excitability.

Inconsistencies with the Standard Hypothesis of Synaptic Control of CN Activity

Despite the apparent success of explaining CN firing levels as a function of SS activity in some situations, we would argue that the translation of activity in CN afferents into patterns of CN firing is not well understood, because in many important situations the evidence suggests that in fact SSs are not the dominant factor controlling CN activity.

First, it is important to note that the above-described manipulations of SS activity also alter other inputs to the CN, in particular, the activity of the olivocerebellar system, and alteration of these inputs may have also contributed to the observed changes in CN activity. Thus, the above findings are not absolutely conclusive with regard to establishing SSs as the dominant modulator of CN activity, even in those conditions. Furthermore, although many PCs show increases in SS activity that are appropriately timed to cause the observed inhibitory portions of CN stimulus-evoked responses, many other PCs respond at similar latencies to the same stimuli with decreased SS activity [20]. Thus, the heterogeneity in the PC response to stimulation of cerebellar afferents makes it difficult to draw any strong conclusions about the relationship of SS to CN activity from population responses, and suggests that instead of recording from individual PCs and CN neurons in separate experiments and infering a relationship between the two populations, one may need to record from synaptically connected PC–CN neuron cell pairs in order to draw any firm conclusions about specific cell-to-cell interactions.

Although the failure to explain the relationship of CN firing to SS activity may be partly due to population heterogeneity obscuring the clear relationships that potentially exist between individual, synaptically coupled PCs and CN neurons, other results that suggest a more fundamental problem also exists. For example, the high spontaneous CN firing rates (30–50 Hz) in waking animals [30, 31], and their similarity to rates in vitro suggests that the relative efficacy of SS activity is weaker than would be expected based on the anatomical data, and is inconsistent with the standard model of SS dominance. More problematic, the predicted inverse relationship is often not found during behavioral tasks. Treadmill walking provides a clear example of this failure, because both SS and CN activity are highest during the same part of the locomotor cycle (swing phase of the ipsilateral limb) [32, 33]. Similarly, during wrist movements SS and CN activity co-modulate [34]. And, although many CN neurons show bursts of activity in relationship to eye and limb movements, the timing of the changes in SS rates are not appropriate or precise enough to explain the sharp transitions that demarcate the bursts in CN firing (e.g., with respect to saccades, see [35]). Lastly, although cooling of the cerebellar cortex increases CN firing rates, the increase is rather modest (<20%) [21]. In sum, the standard model of how CN activity patterns are generated fails to give accurate predictions in many behaviorally important situations.

Alternative Mechanisms for Modulation of CN Activity: Cerebellar Afferents

These failures suggest that there are alternative, or at least additional, mechanisms for controlling CN activity that can be as, or more, important than SS activity. When SS and CN activity are found to co-vary, excitatory drive from collaterals of cerebellar afferents has typically been suggested as a possible explanation [32-34].

However, it would be somewhat surprising for the activity of these collaterals to be more influential in driving CN output than PC terminals, given the dominance of the PC terminals described earlier. Indeed, olivocerebellar axon collaterals account for only about ~5% of CN synapses [36]. Lesion experiments have also suggested that olivocerebellar collaterals only have a weak effect on CN activity [22]. Nevertheless, olivary collaterals clearly can drive

CN activity in certain situations. For example, after injection of harmaline, the resulting tremor partially survives silencing of the overlying cortex by cooling [37]; however, in this situation, the activity of the collaterals is synchronized to an extent that is rarely if ever realized under physiologic circumstances. Under more physiological conditions it would be surprising if olivocerebellar collateral activity could dominate, particularly given that their excitatory effect on CN neurons is always rapidly followed by an inhibitory wave due to CS activity.

Mossy fiber collaterals also can represent only a small percentage of synaptic terminals in the CN, because the terminals of PC axons and olivocerebellar axon collaterals combined already account for ~75% of the total, and the remaining ~25% must be distributed among all of the other non-PC sources. Despite their small numbers, some mossy fibers can generate very high frequency bursts in response to sensory stimuli, and during movement (e.g., see refs [15-17]), and thus might be able to dominate SS activity in those instances. However, in behaving animals, infusion of glutamate blockers into the CN has little to no effect on average firing rates, nor any effect on eye blink conditioning, a behavior that is allegedly dependent on CN function [38]. In sum, although collaterals of cerebellar afferents must have a role in modulating CN activity, it seems unlikely that they would have the dominant role, except perhaps under special circumstances.

Alternative Mechanisms for Modulation of CN Activity: CSs

The apparent inability to explain CN activity only in terms of the activity of cerebellar afferent collaterals and SS activity raises the possibility of an important contribution by CS activity. The possiblity of CS activity having a signficant direct effect on CN activity is not usually considered because of the low average firing rate of CSs relative to SSs, and because CS firing rates are often only weakly modulated during movement. Even in situations where strong modulation of CS firing rates is observed (e.g., see ref [39]), the range of modulation is at most a few Hertz, whereas SSs can vary over a range of close to 200 Hz.

Firing rate, however, may be the wrong parameter to use when investigating the function of the olivocerebellar system, as the organization of this system is clearly geared toward the generation of patterns of synchronous CS activity across populations of PCs [40-43]. Indeed, we found significant changes in CS synchrony in association with licking movements [44] and with whisker movements evoked by motor cortex stimulation [45]. More recently, increases in CS synchrony levels were found in association with locomotion [46, 47]. These results suggest that CS synchrony is a key functional parameter of olivocerebellar function, and that CS activity has a significant effect on cerebellar motor commands, and therefore must significantly affect CN activity.

To test this inference, we sought to quantify the effect of CS activity on CN spiking behavior by recording from large numbers of PCs and CN neurons simultaneously [48]. Using this approach, we have identified CN neurons along with groups of PCs that are presynaptic to them (Lang and Blenkinsop, unpublished results). Cross-correlograms of simultaneously recorded CS and CN activity from such synaptically connected PC–CN cell pairs showed that CSs cause a significant inhibition of CN spike activity. This was true for both burst firing and tonically active CN neurons. The duration of this inhibition can be quite long (>100 ms), exceeding the expected duration of the GABAergic inhibitory postsynaptic potential (IPSP) that was presumably triggered by the CS in the CN neuron. Thus, CS-mediated inhibition may actually cause long-lasting changes in the excitable state of a CN neuron, perhaps by activation or deactivation of intrinsic membrane conductances (see below for further discussion of this possibility).

A Specific Role for CS Activity: Control of CN Bursting Patterns

Under ketamine/xylazine anesthesia the activity patterns of CN neurons range from bursting to tonic [49]. Stereotypical examples of bursting and tonic firing patterns are shown in Fig. 1. Even though spontaneous burst firing is unusually common under ketamine/xylazine anesthesia, CN neurons show burst type activity in many physiological situations, indicating that it is not an anomalous firing pattern due to the anesthesia. For example, CN cells show spike bursts in vitro [3-6, 50-52], and in vivo during various motor behaviors, including locomotion, reaching, and eye movements [32, 33, 53-61], and spontaneously during various states of arousal, particularly slow wave sleep [62, 63].

Clearly, the intrinsic properties of CN neurons give them the potential to display burst type firing; however, control over when such bursts occur, and perhaps additional burst parameters (e.g., intraburst spike frequency and burst duration), are likely shaped by synaptic activity. In fact, for burst firing neurons, a pattern in which CSs primarily occur during the silences that separate the firing bursts of CN neurons is often found (Fig. 1a), and synchronous discharges (see raster) often occur at transitions between these activity states [48]. These results suggest CSs contribute to shaping the bursts of CN neurons, which, given the prevalence of this firing pattern during behavior, implies that CS activity has a significant direct effect on cerebellar motor commands.

However, it is possible that the bursts observed under anesthesia are generated by a distinct mechanism from those occurring during behavior (and in fact, bursts during different behaviors may not all be generated by the same underlying mechanism). In particular, several recent studies have suggested that under ketamine anesthesia, rhythmic bursting activity in various cerebellar elements is driven by neocortical activity related to the slow oscillation in the EEG [13, 49, 64]. Moreover, some of these studies suggested that rhythmic bursts in CN neurons are driven via a cerebro-ponto-cerebellar route [13, 49]. However, the underlying mechanism for this process is not clear, because the phase shifts observed by Schwarz are too long for activity from neocortex to drive CN neurons directly via a simple synaptic relay in the pons [13]. Thus, it is unlikely that excitatory drive from mossy fiber collaterals underlies the relationship, which is consistent with the generally weak effect of collaterals on CN activity described earlier. Alternatively, if the slow EEG oscillation affects SS activity, such modulation could in turn drive the bursting of CN neurons. However, even under conditions where rhythmic multiunit cerebellar cortical activity is correlated with the EEG slow oscillation, SS activity shows little to no correlation [64]. Thus, it is difficult to explain how CN bursts, even if correlated with the slow EEG oscillation, would be driven by either mossy fiber or SS activity.

It is interesting to note that CS activity can be correlated with the slow EEG oscillation [64], and this might explain the correlation of CN bursts with EEG activity. This explanation would not be inconsistent with our proposal of CSs helping to control CN burst activity, although it implies that CS activity is being driven by descending activity from the cerebrum under ketamine anesthesia. There may indeed be some such entrainment, but it is worth noting that the IO can generate slow variations in CS levels even when excitatory or inhibitory input to it is blocked [65, 66], suggesting it has this ability independent of being driven by descending activity from the cortex. Slow waxing and waning of CS can also be observed in spontaneous activity in awake animals (Lang, unpublished data). More importantly for the present issue, characteristics of CS activity under ketamine/xylazine anesthesia are, in general, quite close to those in the awake animal. For example, in both cases CS activity has similar ~1 Hz average firing rates and synchrony distributions [67]. Thus, the relationship between CS activity and CN bursts we observed was present with CS activity whose characteristics were well within a physiologic range, making it plausible that

a similar relationship between CS and CN activity would be found between synaptically connected PC–CN cell pairs in non-anesthetized animals.

CS Synchrony as a Mechanism for Changing the Firing State of CN Neurons

In this last section, we consider the questions of how CS activity can shape the burst firing of CN activity, and if so, what role would SS activity then play. Central to answering the first question is the large convergence in the PC to CN projection, probably on the order of 100:1 [10], because it provides a straightforward mechanism by which synchronous CSs could strongly influence the firing of individual CN neurons. PCs within a narrow, rostrocaudally running strip of cortex converge to the same small region of the CN [68, 69], and we have shown that CS activity among PCs in such cortical strips is highly synchronized [70]. Thus, synchronous CS activity should provide large pulses of inhibition to CN neurons. Indeed, assuming a convergence of ~100 PCs onto a single CN neuron, 40 Hz SS firing rates, and CS synchrony levels of ~10–30%, a synchronous CS discharge would result in a transient three- to eightfold increase in the number of IPSPs occurring per millisecond on the CN neuron.

Because CN neurons have nonlinear membrane properties, such pulses of inhibition could do more than simply produce a quantitatively greater effect on CN activity than the ongoing IPSPs resulting from SS activity. In particular, CN neurons have at least two types of electrical responses that may be preferentially modulated by synchronous CS activity. Following large hyperpolarizations, CN neurons have T-type Ca^{2+} channels that let them generate a rebound depolarization on which bursts of spikes can ride [3-5, 50, 51]. The large hyperpolarization caused by synchronous CS activity should trigger rebound depolarizations more readily than the smaller IPSPs associated with SS activity. Indeed, the bursting activity seen in CN neurons after harmaline is probably due to this mechanism [5]. However, the very high levels of CS synchrony produced by harmaline only rarely occur under physiological conditions. Thus, it is unclear whether, under more normal levels of synchronization, CS activity would generate sufficiently large inhibition to trigger rebound bursts. Indeed, there is some evidence to the contrary [71]. Nevertheless, high levels of CS synchrony do occur in response to strong activation of IO afferent pathways from motor cortex [72], and likely also from strong activation of sensory pathways, and so it is possible that in situations where afferents to the IO are strongly activated (e.g., the sensory feedback triggered by an error in motor performance), CSs could trigger rebound firing in the CN. However, such situations are likely unusual, as most of the time movements are executed correctly. Thus, triggering of rebound bursts is not likely to be the standard mode of CS action on CN neurons if it requires very high levels of synchronization.

Alternatively, CS activity could contribute to the firing pattern of CN neurons by interacting with the plateau potential CN neurons can generate, and which allows them to have sustained spike activity [3-5]. In this case, the pulse of inhibition caused by synchronous CS activity would act to break the plateau, silencing the CN neuron. Thus, a more common mode of action for CS activity may be to terminate bouts of CN firing. Consistent with this possibility, stimuli that mimic synchronous CS activity are able to terminate CN plateau potentials, whereas those that mimic SS activity cannot [4]. Our recent preliminary results suggest that under physiological levels of synchronization CSs primarily act to silence CN neurons rather than to trigger rebound bursts of activity (Fig. 1) [48].

Thus, we propose that CN neurons may enter distinct states of excitability, and that CS activity is at least partly responsible for transitions between these states, more often those from a more excitable to a less excitable state. What would trigger the reverse transitions

(i.e., the onset of a CN burst) is not clear, though it seems reasonable to suggest that activity in cerebellar afferent collaterals might be important in this regard, or perhaps that a subset of very highly synchronous CS discharges could be responsible in some cases.

These states should not be thought of as invariant entities, but rather as jumps in the general excitability of a CN neuron (perhaps analogous to the shifting of gears by the transmission of car engines). Indeed, intraburst firing patterns show a large amount of variation in firing rate, both within individual bursts, and between bursts [73]. SS activity, possibly in conjunction with mossy fiber and olivocerebellar collateral activity, may function to modulate CN firing levels within general limits defined by the intrinsic state of CN neuron (as set by CS activity). In sum, CS activity would help determine when CN neurons are excitable, and SSs (possibly in conjunction with collateral activity) would modulate the specific level of activity during these excitable periods.

In conclusion, the failure to date to explain behaviorally related modulation of CN firing patterns satisfactorily may be attributable to a focus on SS activity as the primary source of control. We propose that both CSs and SSs spikes (and cerebellar afferent collaterals) significantly and directly influence the excitability of CN neurons, but do so in distinct ways. Only by studying their combined actions will we get closer to understanding how cerebellar commands to the rest of the nervous system are generated. The possible roles set forth here for each type of activity are speculative, but would be testable by recordings from synaptically connected PC–CN cell pairs.

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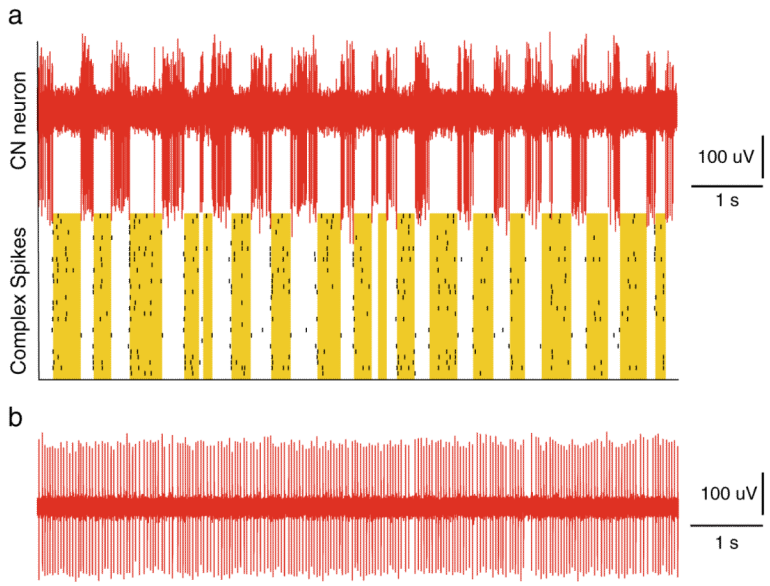

Fig. 1.

CN neurons display tonic and burst firing patterns under ketamine/xylazine anesthesia. **a** Extracellular recording of burst firing CN neuron. Underneath the CN recording, CS activity recorded from 30 PCs simultaneously with the CN cell is shown in raster format. Each *tick mark* represents a CS and each horizontal row of marks contains the spikes from a single PC. The CSs tend to mainly occur when the CN neuron is silent (*yellow-shaded regions*); however, synchronous discharges occur just prior to the ends of some bursts. **b** Extracellular recording of tonically active neuron. CSs were recorded using our standard multiple electrode protocol [74]. The CN activity was isolated using a glass microelectrode that was stereotaxically guided to the CN, and recorded with the same system used to record CSs. Data on the relationship of CSs and CN activity in **a** are based on preliminary findings [48]