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Central Neural Mechanisms Contributing to Cerebellar Tremor Produced by Limb Perturbations

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SUMMARY AND CONCLUSIONS

1. Central mechanisms contributing to cerebellar tremor were studied in three *Cebus* monkeys who were trained to return their arm rapidly to a target region after it was displaced by a perturbation applied to a handle. Cooling through cryoprobe sheaths implanted alongside the dentate and interpositus nuclei resulted in a series of oscillations (tremor) following the perturbation.

2. During progressive cooling from control conditions there was a progressive increase in the number and amplitude of the oscillations and a progressive decrease in their frequency (from 6–8 to 3–5 Hz). The instability of these oscillations and their amplitude and frequency were found to be related to the degree of cerebellar dysfunction.

3. Analysis of EMG activity in biceps and triceps confirmed that during cooling no consistent changes occurred in the segmental (20 ms) and suprasegmental (35–100 ms) reflex responses in the agonist (stretched) muscle, which contributed to the return of the arm following the perturbation. This corrective return was normally actively terminated by EMG activity in the antagonist muscle, occurring 70–100 ms after onset of the torque pulse. During cooling there was a delay in onset of the antagonist activity that resulted in the corrective return overshooting the target. In addition, antagonist activity was prolonged, thus causing a second cycle of oscillation. A similar delay and prolonged burst then occurred in the agonist, and then again in the antagonist, which resulted in continued oscillations.

4. Responses of 74 precentral neurons responding to the torque pulse were studied under control conditions and during cerebellar cooling. Of these, 24 were closely related to activity of either the biceps or triceps muscle in that they had reciprocal responses: inhibition (20–50 ms) followed by excitation (50–100 ms) for one direction of perturbation, and excitation followed by inhibition for the other direction. When the neuron was related to the muscle that was the antagonist, the excitatory second cortical component (cf. intended response (6)) normally appeared in advance of the EMG activity. During cooling no major change usually occurred in the first cortical response, but the second (antagonist related) response was delayed so as to occur after the onset of antagonist EMG instead of before it. Thus the onset of this neural response occurred after the start of muscle stretch, whereas in normal movements it was predictive; that is, it occurred prior to the start of muscle stretch.

5. Following a limb perturbation, return of the limb is brought about, partly by mechanical factors and partly by segmental and suprasegmental stretch reflexes. It is suggested that, in advance of this return, the motor cortex generates a command (the 50- to 100-ms intended response) to the antagonist muscle to terminate the return, on the basis of predictive information provided by the cerebellum. During cerebellar dysfunction the motor cortex does not receive predictive information, but receives only delayed information resulting from stretch of the antagonist muscle. This results in a descending command, which ar-

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rives too late to stop the corrective return and allows it to overshoot the target. It also prolongs the antagonist EMG activity, thus initiating a second cycle of oscillation and subsequent cerebellar tremor.

6. It is thus proposed, first, that cerebellar tremor is a series of alternating stretch reflexes mediated in part through motor cortex, and second, that during normal cerebellar function, the cerebellum breaks this driving by peripheral afferent stretch responses by providing to the motor cortex a predictive signal for the antagonist muscle, which is phase advanced.

INTRODUCTION

Recently we presented evidence that supports the view that cerebellar tremor is due not to some central neural network behaving as an oscillator, but rather to some form of instability in long-loop reflexes (17). For example, we reported that changes in the mechanical state of the limb affect the frequency and amplitude of cerebellar tremor, and that perturbations applied to the limb resynchronize the phase of the tremor. It was also concluded that cerebellar tremor could not result from excessive gain in these reflex loops because no correlation was found between the size of the segmental and suprasegmental reflex responses to a limb perturbation and the tendency toward oscillation during cerebellar dysfunction.

What then could be the cause of cerebellar tremor? Under normal conditions occasional damped oscillations at 6–8 Hz are observed when monkeys make arm movements about the elbow or when perturbations are applied to the limb (4, 5, 17). During cerebellar dysfunction, a prolonged series of oscillations occurs in both situations at a frequency of 3–5 Hz. One suggestion that would explain the decrease in frequency during cerebellar dysfunction is that there is an increase in delay in a long-latency servo pathway through motor cortex. If this were the case, one might expect an increase in latency in the response of motor cortex neurons to a limb perturbation during cerebellar nuclear dysfunction. When cooling was applied to the lateral dentate (11) or to medial dentate and interpositus nuclei (18), no major change was observed in the first cortical response (20–50 ms) to a limb perturbation. However, a decrease was observed in the magnitude of the second cortical response (50–100 ms) which, in another experimental situation (6), was correlated with the intended response and was dependent on prior instruction.

The present study was undertaken to investigate more closely the relationship between this second cortical response and the development of cerebellar tremor. The results described here suggest that this second cortical (intended) response is a predictive instruction from the cerebellum, relayed by motor cortex to the antagonist muscle, to terminate the return of the limb following the perturbation. During cerebellar dysfunction this second cortical response is blocked, which causes the servomechanism through motor cortex to be driven only by afferent feedback from the periphery. This results in delay in motor cortex discharge and delay in onset of the antagonist muscle. This in turn allows an overshoot of the corrective return movement to occur. A series of such overcorrections is observed as cerebellar tremor.

METHODS

Three *Cebus* monkeys (*M28L*, *M51L*, *M54L*) were trained to hold a handle, pivoted at the elbow, stationary within a target window of 10–20° and to resist torque pulses (40 ms, 100 g) applied to the handle at random times. If the perturbations displaced the handle outside the window, monkeys were rewarded only if they returned the handle to the target within 200 ms. The target was displayed to the monkey as a vertical band on an oscilloscope screen. The width of the band indicated the width of the target window. Handle position was displayed by a narrow vertical line.

Two cryoprobe sheaths (1.3 mm in diameter) were implanted under pentobarbital anesthesia (35 mg/kg ip) ipsilateral to the tested arm, one lateral to the dentate (coordinates: P6.5, L7.0, V−5.0), the other through the region of the interpositus (P8.0, L3.0, V−4.0). These will be referred to as the lateral and medial sheath, respectively. The sheaths were inserted at caudorostral angles of 40° to the vertical (lateral sheath) and 20° (medial sheath) in a parasagittal plane and were pushed past the targets by 2 mm. Temperatures were measured by a thermocouple attached to the outside of the sheath, 4 mm from its tip.

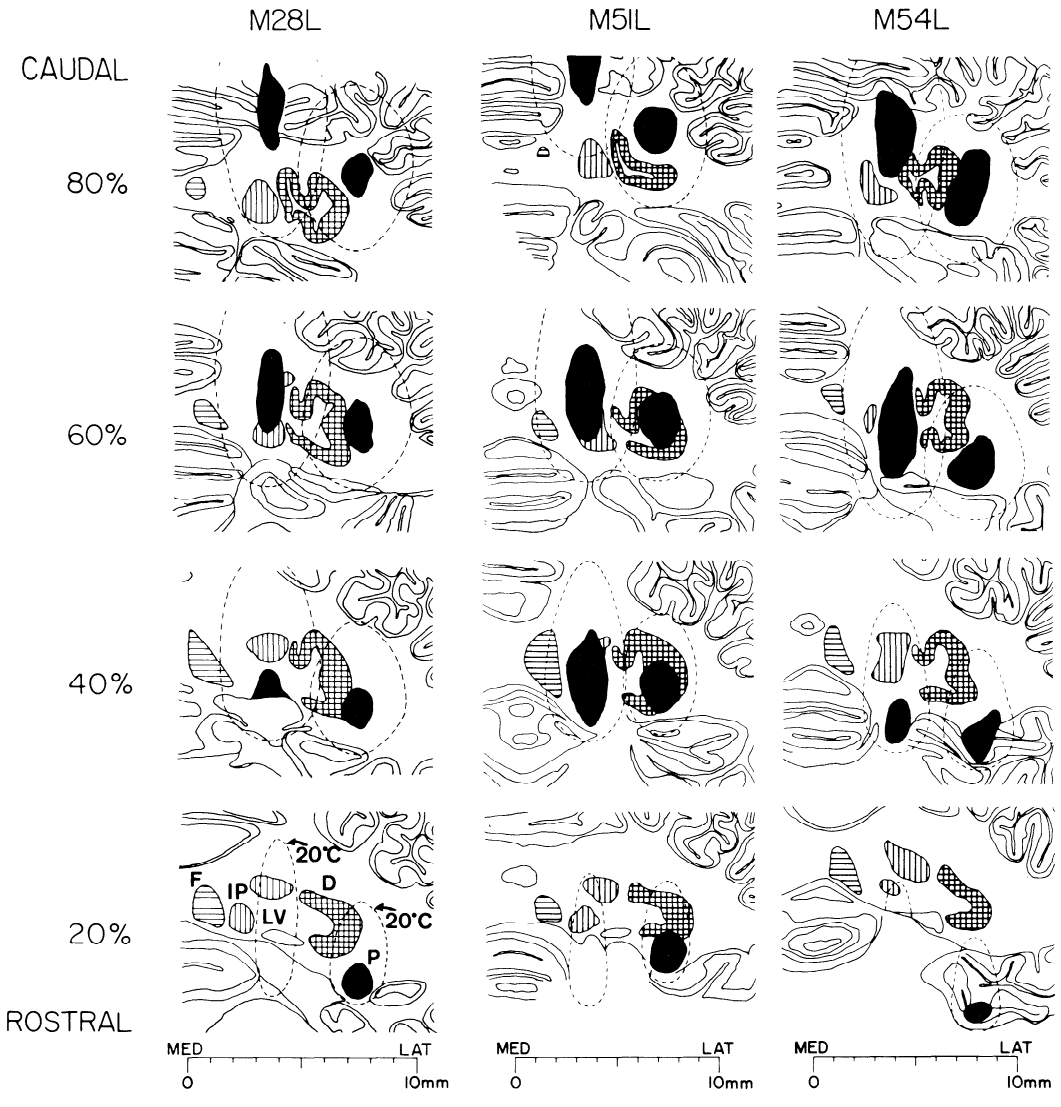

FIG. 1. Positions of medial and lateral cooling probe sheaths in *M28L*, *M51L*, and *M54L*. Frontal sections are shown for each monkey at 20, 40, 60, and 80% of the rostral-caudal extent of the dentate nucleus. Dotted lines are estimated isotherms for tissue temperature of 20°C when sheath reference temperature was 10°C. Midline is the left border of each section. D, dentate nucleus (cross hatching); IP, interpositus nucleus (vertical hatching); F, fastigial nucleus (horizontal hatching); LV, lateral vestibular nucleus (unshaded); P, sheath probe position (black).

Histological confirmation of sheath positions was obtained after killing the animal by intraperitoneal injection of pentobarbital and perfusion with 10% formalin. Figure 1 shows the location of the sheaths and the extent of the estimated 20°C isotherms (3), the temperature at which synaptic transmission is said to be first impaired (1, 2). The isotherms indicate that when the lateral sheath was cooled to 10°C, the lateral portion of the dentate nucleus was affected in all three monkeys. Cooling the medial sheath to 10°C affected the medial portion of the dentate and a major part of the interpositus. In addition, cooling the medial probe may have affected transmission in the fastigial and lateral vestibular nuclei.

Under pentobarbital anesthesia a metal chamber for extracellular single-unit recording was implanted, in the three monkeys, over the arm area of the precentral gyrus. This area was located by determining the region from which movements about the elbow joint were evoked at the lowest threshold of surface stimulation.

Three response parameters, timed from the

torque pulse, were digitized on-line and stored on magnetic tape using a PDP-11/40 computer. These were *1*) handle position from a thin-film potentiometer; *2*) EMG activity recorded with a pair of Teflon-coated stainless steel wires inserted into biceps and triceps, then amplified, filtered (bandwidth 30–300 Hz), and full-wave rectified; and *3*) unit activity recorded with glass-coated platinum-iridium electrodes. Unit activity was stored as event times with a resolution of 2 ms and block averaged into 10-ms bins. Block averaging of the EMG data into 10-ms bins resulted in digital integration.

RESULTS

Effect of varying degree of cooling on cerebellar tremor

All three monkeys eventually displayed large-amplitude undamped oscillations about the elbow following perturbations applied to the limb during simultaneous cooling through both probes. However, it was only after some weeks of experiments, in which cooling was applied while monkeys held the handle on target or moved it between targets, that this tremor following perturbations became marked. It is possible that this delay in development of tremor results *1*) from additional cerebellar nuclear damage produced by cooling, *2*) from monkeys making less goal-directed movements (8) in the first few weeks following implantation, or *3*) from some central compensation for the lesions.

In a previous paper (17) the amplitude and frequency of tremor were found to vary with different mean positions of the arm and with different mechanical loads applied to the handle. In the present experiments these external conditions were kept constant while the degree of cerebellar dysfunction was varied. The latter was achieved by varying the amount of cooling through the medial and lateral cryoprobes. When cooling was turned on, probe-tip temperature reached the preset steady-state level within 1 min. On termination of cooling, probe-tip temperature returned to normal within about 2 min.

Figure 2*A* illustrates typical responses of the arm after the application of a randomly timed torque perturbation. With the cerebellum at normal brain temperature, the arm returned the handle to the original position, either as a single smooth movement or with one or two oscillations. Occasionally these oscillations continued and took the form of a small-amplitude 6- to 8-Hz tremor (*A*, top record). This high-frequency tremor seemed to be more prevalent at the beginning of an experiment when the monkey was anxious for juice reward or toward the end of an experiment when the animal was tired.

After cooling was started, a gradual increase in the number and amplitude of the oscillations following the perturbation was observed (Fig. 2*B*). This was accompanied by a gradual decrease in the frequency of the oscillations. On stopping the cooling, a progressive reversal of these changes occurred (Fig. 2*C*). If the temperature was allowed to stabilize at a particular value, a fairly constant degree of instability was observed. The instability was greatest at the lowest temperatures (Fig. 3*D*, *E*, *F*). The degree of instability at a particular temperature varied in the three monkeys, with *M51L* requiring the least cooling (15°C) and *M54L* requiring the most cooling (5°C) to reach the same degree of instability. This factor seemed to be related to probe placement. Histology (Fig. 1) shows that in *M51L*, the monkey with the greatest instability, the lateral probe was implanted through the dentate rather than adjacent to it. Cooling either the medial or lateral probe singly produced a smaller degree of instability than if both probes were cooled together (Fig. 3*B*, *C*, *D*).

The decrease in frequency with cooling was thought not to be the direct result of the increase in the amplitude of the oscillations. This is because the addition of viscous resistance (friction) to the handle had previously been shown to decrease the amplitude of the oscillations without affecting the frequency (17). This was confirmed in the present experiments.

Effects of cooling on EMG responses

Accompanying these changes in the stability of the monkey's response to the torque pulse during progressive cooling, there were progressive changes in the EMG responses of the biceps and triceps muscles. The agonist EMG response to stretch consisted of the well-known early activity, i.e., M1, M2, M3 responses, latency 20–100 ms (15), and one or more later bursts starting

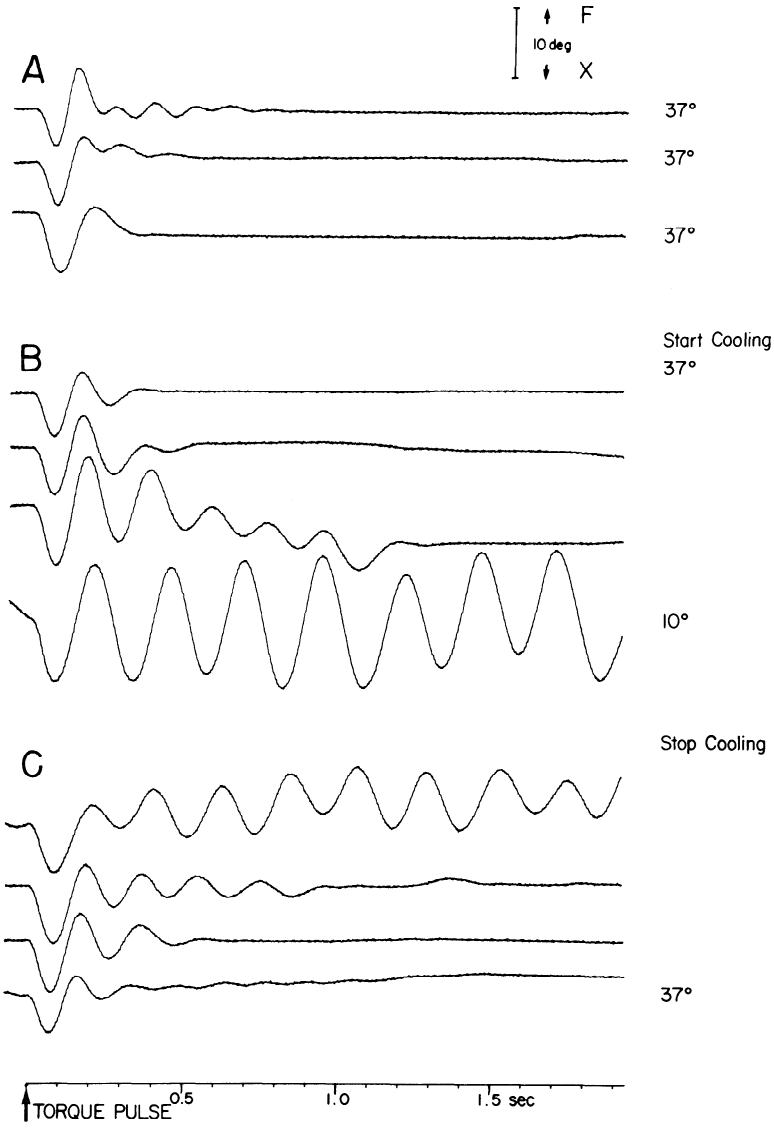

FIG. 2. Selected records to illustrate the effect of progressive cooling on handle position following a perturbation. *A*: control. *B*: simultaneous cooling of both probes produces a progressive increase in the number and amplitude of oscillations and a decrease in frequency. At 10°C there is an undamped tremor as the monkey attempts to hold the handle in target. *C*: cooling is stopped and there is a progressive reversal to control conditions. Temperatures are those of both sheaths measured 4 mm from the tip (*M51L*). Vertical bar at top of figure indicates target width of 10°. *F*, toward flexion; X, toward extension.

150–200 ms after the torque pulse. The early agonist EMG response contributed to the corrective return of the arm back toward its original position. This return was then terminated by onset of antagonist EMG activity (latency 70–100 ms) timed to occur slightly before or just after the beginning of antagonist stretch.

Cooling through medial and lateral probes produced little or no consistent change in the M1, M2, M3 responses in the agonist, as previously reported (17). The earliest significant change during cooling occurred in the antagonist. As the temperature was lowered there was a progressive delay in the onset of antagonist activity. This is shown

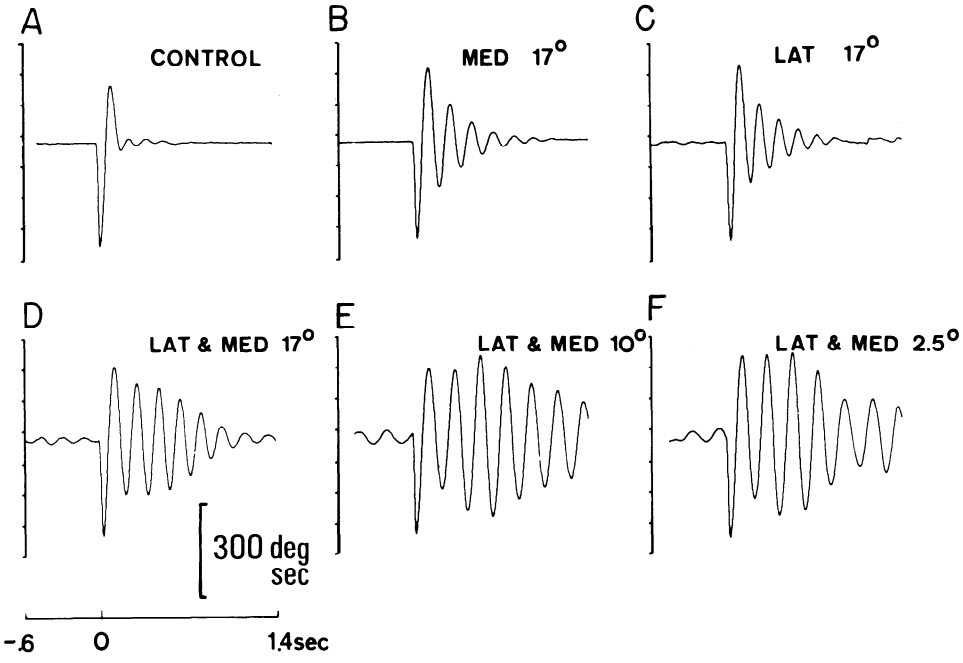

FIG. 3. Velocity of movement averaged with respect to a flexion load torque pulse applied at time zero. Each trace represents the average of 20 movements obtained after cooling had stabilized. Temperatures, shown in degrees centigrade, are those of the implanted probes; med, medial; lat, lateral (*M28L*).

for control and cooled situations in Fig. 4. This delay was accompanied by a larger overshoot of the corrective return movement (stretch triceps). In addition, antagonist activity was prolonged, thus initiating a movement back in the opposite direction. A similarly delayed and prolonged burst now occurred in the agonist, thus continuing the

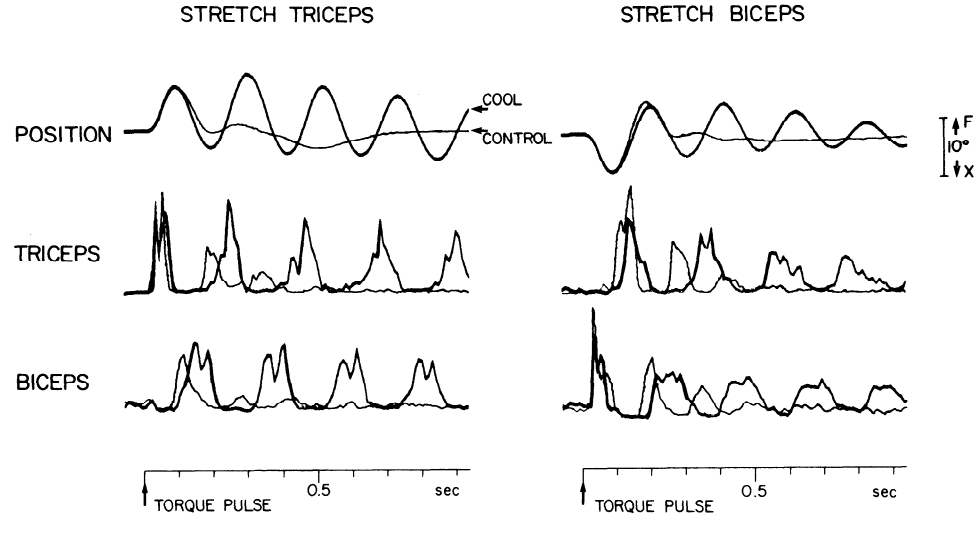

FIG. 4. Effect of cerebellar nuclear cooling on position and EMG activity in biceps and triceps following a perturbation applied to the stationary limb. Each trace represents the average of 25 trials. Thin line, control; thick line, cerebellar nuclear cooling (medial and lateral sheaths, 10°C). Note during cooling a delay and a prolongation occur initially in the antagonist, and in both agonist and antagonist in subsequent oscillations (*M51L*).

sequence of overcorrections and producing undamped oscillations or tremor. It should be stressed that, in cases where the control trials had overshoot of the return movement (Fig. 4, stretch biceps), changes in the position record during cerebellar cooling only became clear in the second cycle.

Thus, an apparent requirement for stable corrective return movements is that EMG activity in the antagonist be initiated sufficiently in advance of the forearm reaching its desired position. This does not occur without proper function of the cerebellum. When cooling disrupts cerebellar function, corrective movements must rely on stretch reflexes to terminate the return movement, which then results in movement overshoot. However, in order to generate unstable corrections or tremor, an additional factor must come into play. To generate tremor the activity of the antagonist must be large enough, not only to terminate the movement, but also to turn it around, thus starting another cycle of oscillation. Such a prolongation of antagonist EMG activity could result from a delayed long-latency reflex through motor cortex.

Related precentral neuron activity during cerebellar tremor

To determine the role of the motor cortex in the production of cerebellar tremor, a comparison of the timing of activity of precentral neurons, which responded to the muscle stretch, was made during normal corrections and during overcorrections caused by cerebellar cooling. In penetrations through the elbow region of motor cortex, recordings were made from several hundred neurons. Of these, 74 responded clearly to limb perturbations and were analyzed in detail (6 in *M28L*, 44 in *M51L*, and 24 in *M54L*). Of this total, 24 neurons showed a pattern of activity that was closely related to the pattern of EMG activity of either the biceps or triceps muscles. This pattern during normal movement corrections has been described previously by others (4, 6, 7) and is as follows. These units all responded with an early change in activity that was reciprocally related to the direction of initial stretch (Fig. 5). If a unit had a first excitatory response (latency 20–50 ms) (Fig. 5*A*) to one direction of stretch, this excitatory activity was followed by an inhibitory or silent period. When the opposite direction of stretch was applied, the first response was now inhibitory or silent and was followed by a period of excitation (latency 50–100 ms) (Fig. 5*C*).

The activity of these reciprocal neurons could be related to the activity of a particular muscle. For example, for one direction of stretch, when the muscle was stretched and was the agonist, the first precentral excitatory activity occurred before the M2 and M3 EMG responses (Fig. 5*A*). For the opposite direction of stretch, when this muscle was the antagonist, the late precentral excitatory activity occurred before the onset of this antagonist EMG (Fig. 5*C*). Thus the pattern of activity of these cells was consistent with their taking part in a servomechanism through motor cortex. The remaining neurons had a variety of other patterns and will be discussed later.

As described earlier, in the control situation, the return after a perturbation was initiated in part by segmental and suprasegmental EMG responses. A stable return was usually terminated by EMG activity in the antagonist. When related to the antagonist, these servolike units responded with a burst of activity that preceded activity in the antagonist muscle. Furthermore, this burst frequently occurred before stretch of the antagonist muscle. If subsequent oscillations occurred, the onset of EMG was preceded by activity in the related precentral neuron. Similarly, in the subsequent corrections, the onset of this cortical activity was prior to the stretch of the muscle to which they may be servo linked (Fig. 5). In these servolike units and other units that had clear timing relationships between cell activity and EMG, there was frequently little relationship between the magnitude of EMG response and the magnitude of the corresponding responses in the cortex.

Cooling through both probes simultaneously usually had little effect on the first cortical response: 3 units showed an increase, 6 a decrease, and 15 were unaffected. However 17 of the 24 reciprocal neurons showed a striking delay in the onset of the second cortical response. This delay was clearly observed when the second cortical response was excitatory, that is, when it was related to the discharge of the antagonist

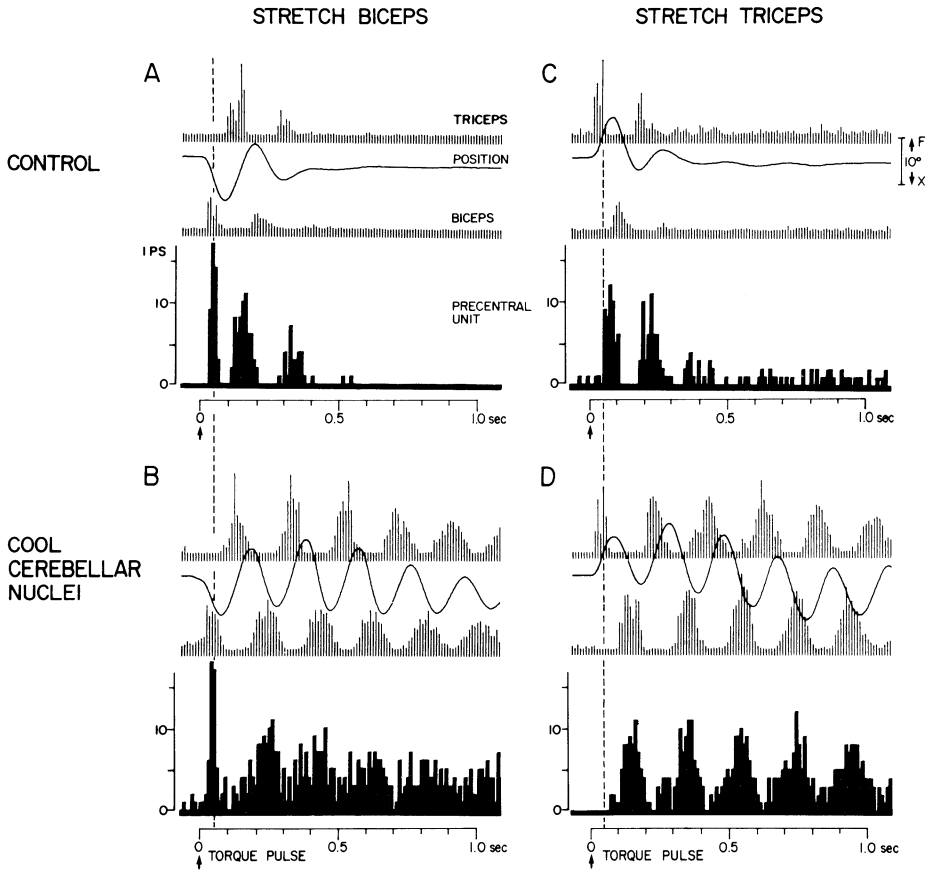

FIG. 5. Effect of cerebellar nuclear cooling on a reciprocal precentral neuron and the corresponding position and EMG records. Unit is closely related to EMG of biceps muscle. During cooling there is no change in the first cortical response (20–50 ms), which could contribute to the largely unchanged late stretch reflex responses in biceps (left side during biceps stretch). However, there is a major delay in the second cortical response (50–100 ms) (right side during triceps stretch) when biceps is the antagonist. During cooling unit is no longer phase advanced to the onset of biceps activity, but now follows biceps stretch. Dashed line, at 50 ms, drawn for reference. Each record represents the average of 25 trials. IPS, impulses per second (*M51L*). Cerebellar cooling with both medial and lateral sheaths at 10°C.

muscle. This is shown for a reciprocal unit in Fig. 5. Instead of occurring at 70 ms, prior to stretch of the antagonist and prior to onset of antagonist EMG (Fig. 5*C*), the second response was delayed during cooling (Fig. 5*D*) so as to occur after the onset of stretch. At this time it could only prolong an already delayed EMG activity. This same delay occurred for all these reciprocal units in subsequent oscillations in that the peak of unit activity followed rather than preceded the start of muscle stretch. This result differs from that of others (11) where no change was reported in the phase lead of precentral units to the movement before and during dentate cooling. During cooling in the present study, EMG activity in the muscle being stretched, started 10–20 ms after the start of stretch and was probably relayed by short-latency segmental stretch reflexes. Cortical activity did not occur until late in the EMG activity, and thus possibly contributed to its prolongation. This prolonged EMG response, in turn, initiated another cycle of oscillation.

The remaining 50 units showed a variety of response patterns. In some, the first response was not reciprocal; that is, it was either excitatory or inhibitory for both directions of initial stretch. Others did not show

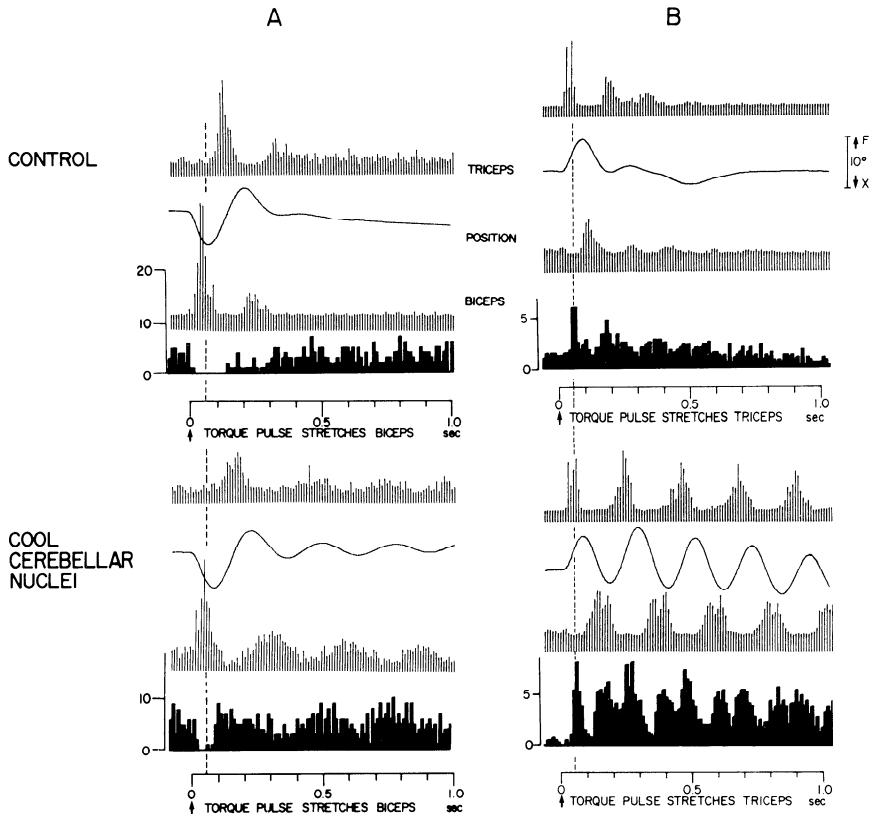

FIG. 6. Example of two nonreciprocal precentral neurons and the corresponding position and EMG records. *A*: a neuron that exhibited an inhibitory first response for either direction of stretch (*M54L*). *B*: a neuron that exhibited an excitatory first response for both directions of stretch (*M51L*). Bottom records in *A* and *B* illustrate the effect of cerebellar dysfunction. Each record represents the average of 25 trials. Cerebellar cooling with both medial and lateral probes at 10°C.

a distinct period of inhibition (latency 50–100 ms) following the first excitatory response or, conversely, if the first response was inhibitory, it was followed instead by a second period of inhibition. Of these 50 units, 22 had excitatory second responses, 12 of which showed a decrease with cooling, 3 an increase, and the remaining 7 no change. These figures are comparable to those of previous experiments (11, 18).

Although these 50 neurons all exhibited changes in their firing patterns during cooling, these changes were frequently difficult to interpret. Examples of two such cells are illustrated in Fig. 6. The cell in Fig. 6*A* showed inhibitory first and second responses for both directions of stretch. Cerebellar cooling had little effect on the first response, but produced disinhibition of the second response. It may have been expected that this unit would be modulated for both directions of stretch during cerebellar cooling. However, the unit shows only weak modulation during stretch in one direction. Figure 6*B* illustrates a cell that showed an excitatory first response for both directions of stretch. No distinct second response was observed. During cooling two periods of excitation were observed; one following biceps stretch, the other following triceps stretch. However, since the first response was nonreciprocal, it is also possible to interpret this activity as leading the next cycle of stretch. Thus the changes in firing pattern that occurred in this neuron during cerebellar cooling may simply be a consequence of the different movement pattern and not a direct effect of cerebellar

dysfunction. Only 14 of these 50 neurons had distinct modulation of their activity during cerebellar tremor, as opposed to all 24 neurons of the type illustrated in Fig. 5. The absence of modulation in the remaining 36 neurons may be due to an absence of excitatory peripheral input from the oscillating limb, as in the cell illustrated in Fig. 6*A*, or may indicate that their activity was related to joints that did not undergo tremor.

DISCUSSION

A computer simulation based on a synthesis of experimental data suggested that cerebellar intention tremor may be related to instability in suprasegmental reflex pathways involving a servomechanism through motor cortex (13). However, there was one problem with this suggestion. The decrease in the frequency of oscillations from 6–8 to 3–5 Hz suggested that an increase in delay occurs in this pathway. However, unit recording in motor cortex with either reversible lesions of the lateral dentate (11), medial dentate and interpositus (18) or, as in the present study, a combination of both, indicates that the first cortical response (20–50 ms) to a perturbation is largely unaffected by cerebellar nuclear lesions. The earliest component to be affected occurs at a latency of 50–100 ms. On the basis of these results it is puzzling how a lack of the second, but not the first component, could result in a delay that produces a decrease in frequency.

Our present results suggest a new interpretation for the function of this second cortical component. During movement correction after a torque pulse perturbation, an excitatory second cortical response can be related to the activity of the antagonist muscle, which normally causes the return movement to be terminated promptly. During cerebellar dysfunction this second cortical component is blocked and the correction is now terminated by reflex pathways, both segmental and suprasegmental via the delayed second cortical response. This delayed cortical response does not reach peak activity until a significant amount of stretch has occurred. Presumably this is because the return movement, unlike the initial perturbation, is not an abrupt stretch (cf. Fig. 8, Ref. 17), and the afferents driving it may be position and velocity sensitive rather than acceleration sensitive. Because it is delayed, its contribution to motoneurons only prolongs activity already initiated by shorter latency reflex pathways. This prolonged activity initiates the start of a second cycle of oscillation, which in turn is arrested and reversed by prolonged stretch reflexes in the opposite muscle. A series of such alternating stretch reflexes results in tremor.

In view of this result, it is not surprising that the character of this tremor will be affected by mechanical loads applied to the limb (17). After the initial perturbation, the velocity of the return will be determined in part by segmental and suprasegmental stretch reflexes, and in part by the mechanical properties of the muscle, forearm, and handle. If the handle mechanics are altered by the addition of inertia, viscosity, or elastic stiffness, the velocity of the return movement will be affected. This will alter the afferent information reaching motor cortex and will alter its contribution to the stretch response. For example, addition of inertia would slow the return movement. Thus motor cortex activity, which during cooling is driven by afferent feedback, would be delayed and its contribution to the stretch reflex would be delayed. This would result in a decrease in the frequency of intention tremor oscillations, which in fact was observed (17).

During normal function, the cerebellum seems to break this reliance on stretch responses by providing to the motor cortex information that is phase advanced in relation to the movement. There are two possibilities, not mutually exclusive, of how this may occur. One is that the cerebellum generates a predictive response on the basis of afferent information. It is suggested that the cerebellum can predict what position the forearm will be in the future by knowing the present velocity. Similarly, future velocities can be predicted on the basis of present accelerations. Thus one possibility is that the cerebellum performs single or multiple differentiation, converting an afferent signal, which is related to position or velocity, to one that is related to velocity or acceleration. A feedforward inhibitory mechanism

has been proposed that may serve this function (16). Afferent information would be projected directly to cerebellar nuclei and through a delay to Purkinje cells. The Purkinje cells would inhibit cells in the cerebellar nuclei, which are driven by afferent information. This process would accentuate changing levels of afferent information and inhibit tonic levels. This "differentiated" signal could then contribute to the second response in the motor cortex.

A second possibility is that the phase advance is determined by some predictive mechanism that is based on learning. Evarts and Tanji (6) demonstrated that the second cortical response was related to prior instruction or set of the animal. This response did not depend on afferent input, but on the movement the monkey intended to perform. A similar response, occurring prior to that in the precentral cortex, has been recorded in the dentate nucleus (14). In our monkeys, although the timing of the perturbation was unexpected, its amplitude and direction were not. The cerebellum, with sufficient practice, could learn the appropriate response to terminate the correction. Thus in both experimental situations the second cortical discharge was related to the intended response: in the case of Evarts and Tanji it depended on the direction the monkey was to push, and in our case it was related to activity of the muscle that stopped the limb in the target. This response could be learned in terms of memorizing appropriate timing or more generally, by means of efference copy (10). The latter could function as follows (see Fig. 7*A*). After a perturbation, a correction is initiated by segmental and suprasegmental stretch reflexes involving motor cortex. Since the timing of the perturbation is unexpected, there is little predictive contribution other than perhaps to set the reflexes to resist the direction of initial stretch. The signal from motor cortex, the first cortical response (20–50 ms), in addition to descending to the spinal cord, is sent to the cerebellum. Such a projection has been suggested from work in the cat (12). The cerebellum, on the basis of some model of the forearm, generates an appropriately timed command and sends it to units in motor cortex related to the antagonist muscle. This short cut initiates contraction

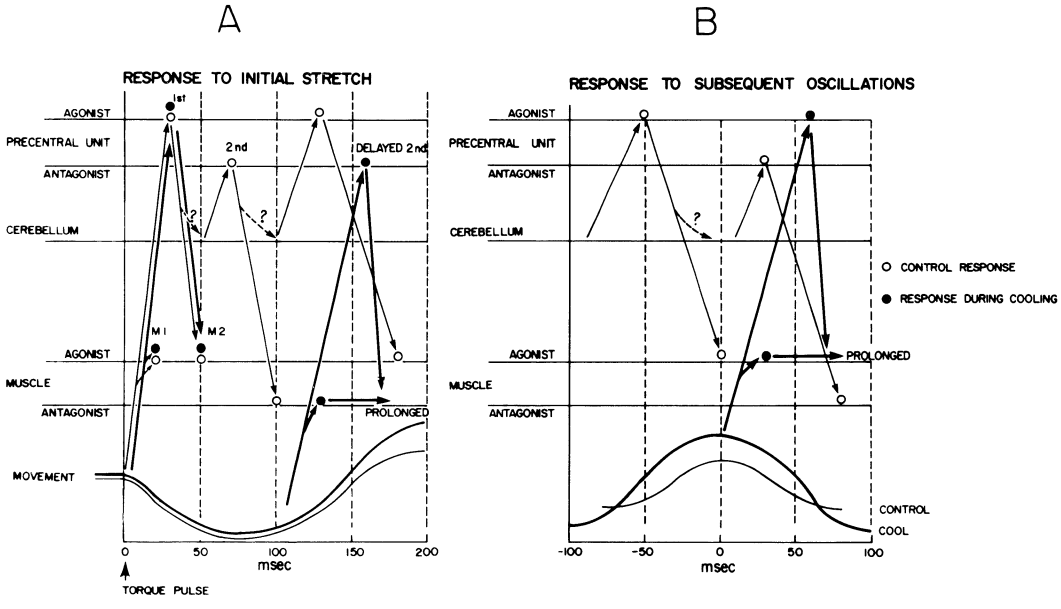

FIG. 7. Summary of proposed cerebellar function in generating commands that are properly timed to terminate corrective movements. *A*: cerebellar contribution following the initial stretch. *B*: cerebellar contribution during subsequent oscillations. Open circles and thin lines are used to denote the sequence of responses in the muscles, cerebellum, and precentral cerebral cortex when the cerebellum is intact. Filled circles and thick lines are used to represent the sequence during cerebellar dysfunction.

of the antagonist in advance of the movement reaching the target position. In addition, possibly by means of reciprocal inhibition, either at the motor cortex or spinal cord, an inhibition of the long-loop stretch reflex occurs. This prevents the EMG activity from being prolonged and thus acts to minimize the initiation of subsequent oscillations. However, if the model is in error due to lack of learning or, as in the case of *M51L*, permanent lesion of part of the cerebellar nuclei, some overshoot may still occur and one or more subsequent oscillations may result. Again during these oscillations (see control, Fig. 7*B*) the activity of precentral neurons, as a consequence of the cerebellar contribution, will be in advance of the start of stretch of the appropriate muscle, the muscle will contract early, and reciprocal inhibition will prevent prolongation of activity. As a result of these two factors, movements will eventually stabilize.

The above mechanism suggests a novel origin for the high-frequency tremor at 6–8 Hz that is occasionally seen in movements when the cerebellum is intact. Our hypothesis suggests it results from an inappropriate cerebellar contribution to the servomechanism through motor cortex. If this contribution is based on internal prediction, memory, or efference copy, the frequency of this tremor, unlike cerebellar tremor, should be relatively independent of mechanical loads applied to the forearm.

The results of the present experiments strongly suggest that peripheral afferent input to motor cortex is involved in the generation of cerebellar tremor. Yet it has been reported by others that after a lesion of the pyramidal tract (8) or removal of peripheral feedback by deafferentation (9), an animal with a cerebellar lesion may still have tremor. We interpret these latter results, not as evidence against the role of peripheral feedback and the motor cortex in the production of cerebellar tremor, but rather as evidence that there are a number of central and reflex loops which, with the appropriate lesions, can become unstable and produce tremor. Undoubtedly cerebellar tremor is a complex phenomenon that may involve activity in many brain areas and output via many descending pathways. The present results indicate that, at least under certain experimental conditions, motor cortex is one area that appears to contribute to the generation of cerebellar tremor.

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