Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex

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The cerebellum has a medial, cortico-nuclear zone consisting of the cerebellar vermis and the fastigial nucleus. Functionally, this zone is concerned with whole-body posture and locomotion. The vermis classically is thought to be included within the “spinocerebellum” and to receive somatic sensory input from ascending spinal pathways. In contrast, the lateral zone of the cerebellum is included in the “cerebro-cerebellum” because it is densely interconnected with the cerebral cortex. Here we report the surprising result that a portion of the vermis receives dense input from the cerebral cortex. We injected rabies virus into lobules VB–VIIIIB of the vermis and used retrograde transneuronal transport of the virus to define disynaptic inputs to it. We found that large numbers of neurons in the primary motor cortex and in several motor areas on the medial wall of the hemisphere project to the vermis. Thus, our results challenge the classical view of the vermis and indicate that it no longer should be considered as entirely isolated from the cerebral cortex. Instead, lobules VB–VIIIIB represent a site where the cortical motor areas can influence descending control systems involved in the regulation of whole-body posture and locomotion. We argue that the projection from the cerebral cortex to the vermis is part of the neural substrate for anticipatory postural adjustments and speculate that dysfunction of this system may underlie some forms of dystonia.

motor system | virus tracing

Classically, the cerebellum is divided anatomically into three cortico-nuclear zones: a medial zone consisting of the cerebellar vermis and fastigial nucleus, an intermediate zone consisting of paravermal cortex and interposed nuclei, and a lateral zone consisting of the most lateral cerebellar cortex and the dentate nucleus (1, 2). Each of these zones is considered to be functionally distinct. For example, lesions of the vermis result in deficits in whole-body posture and locomotion, whereas lesions of the lateral zone result in deficits in limb movements (2, 3). Current texts include the vermis in the “spinocerebellum” and emphasize that it receives somatic sensory inputs related to the head and proximal parts of the body from ascending spinal pathways. In contrast, the lateral zone is included in the “cerebro-cerebellum” because it is densely interconnected with the cerebral cortex (4).

We have begun to examine the inputs to the cerebellar cortex using retrograde transneuronal transport of rabies virus (RV) (5). In the course of these experiments we made the surprising observation that the primary motor cortex (M1) and several of the cortical motor areas on the medial wall of the hemisphere provide a major source of input to lobules VB–VIIIIB of the vermis. Furthermore, a substantial portion of this input comes from cortical regions involved in the control of distal as well as proximal limb movements. Thus, our results challenge the classical view of the vermis and indicate that it no longer should be considered as entirely isolated from the cerebral cortex. Instead, lobules VB–VIIIIB represent a site where the cortical motor areas can influence descending control systems involved in the regulation of whole-body posture and locomotion.

Results

We injected a combination of RV and the β subunit of cholera toxin (CTb) into multiple lobules of the cerebellar vermis (Figs. 1 and 2)

in seven monkeys. In four of these animals, the injections were confined largely to lobules VB–VIIIIB of the vermis. Our results are based largely on the data from these animals. In the remaining three animals, the injections primarily involved more posterior lobules of the vermis but also minimally involved portions of lobules VB–VIIIIB. The data from these three animals are included in the composite maps presented later in the results. All tracer injections were made on or to the right of the cerebellar midline. This report focuses on cortical neurons labeled in the left hemisphere.

We set the survival time following the virus injections at 42 h to allow for two stages of retrograde transneuronal transport (7). In the first stage of transport, virus was taken up by axon terminals of neurons at the injection site in the vermis and transported in the retrograde direction to label first-order neurons in the pons. The location of the pontine neurons labeled by retrograde transport of CTb to these first-order neurons was consistent with the results of prior studies of pontocerebellar input to the vermis (8, 9). Then, in a second stage, virus was transported transsynaptically in the retrograde direction from first-order neurons in the pons to label second-order neurons in the cerebral cortex. In fact, we found that all the cortical neurons that were labeled after virus injections into the vermis were located in layer V. The laminar location of these neurons is the same as the location of cortico-pontine neurons labeled by retrograde transport of conventional tracers from the pons (10). We did not find any labeled neurons in cortical layers above or below layer V. This observation confirms that the survival time was long enough to allow transneuronal transport of virus from the vermis to second- but not third-order neurons in the cerebral cortex.

Cerebral Cortex Projects to the Vermis. Our major observation is that retrograde transneuronal transport of virus from lobules IV–IXA of the vermis labeled large numbers of neurons in the cerebral cortex (Figs. 3–5). The total number of neurons labeled in the cerebral cortex after retrograde transneuronal transport of virus from the vermis averaged 10,384 neurons (measured on every fourth section; range, 4,982–16,350, $n = 4$). In comparison, the total number of neurons labeled in the cerebral cortex after retrograde transneuronal transport of virus from comparable-sized injections into the cerebellar hemisphere averaged 14,472 neurons (range, 4,597–29,775, $n = 4$) (data from ref. 5). The difference in these averages is not statistically significant (unpaired student's t test). The density of labeled neurons in areas of the cerebral cortex following transneuronal transport of virus from the vermis also was comparable to that following transneuronal transport from the hemisphere. It has long been recognized that the cerebral cortex provides a major input to the hemisphere. Thus, our observations suggest that the cerebral cortex is a major source of input to the vermis.

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Fig. 4. Origin of projections to lobule VIII of the vermis (M18). The frontal lobe is displayed with the medial wall of the hemisphere reflected upwards. The map begins at the frontal pole and continues caudally to the intraparietal sulcus (IpS). The cingulate sulcus is unfolded to display the location of labeled neurons on its dorsal (CgSd) and ventral (CgSv) banks. Colored bins indicate the number of labeled neurons in 200- μ m bins throughout the cerebral cortex. The number of cells per bin was divided into five levels that are color-coded: white, top 5% of bins (95–100%); yellow, 90–95%; red, 80–90%; and blue, 40–80%. Bins containing 0–40% of cells are omitted. ArS, arcuate sulcus; C, caudal; CC, corpus callosum; CgG, cingulate gyrus; CgSd, cingulate sulcus, dorsal bank; CgSv, cingulate sulcus, ventral bank; CMAr, rostral cingulate motor area; CMAv, ventral cingulate motor area; CS, central sulcus; D, dorsal; IpS, intraparietal sulcus; LS, lateral sulcus; M1, primary motor cortex; PMd, dorsal premotor area; PMv, ventral premotor area; S1, primary somatosensory cortex; SMA, supplementary motor area.

6). The peak density of labeled neurons was located in the trunk representation (between the arm and leg representations) and extended into the axial body representation of M1 according to Woolsey's map (lateral to the yellow arrow in Fig. 6). This region includes a portion of the arm representation of the PMd in more current maps (11, 14) and a laterally placed region recently shown to influence muscles involved in eyelid closure (15). Overall, ~85% of the labeled neurons were located in regions of proximal/axial representation. The proximal/axial emphasis in the origin of inputs from M1 also is apparent in the maps from individual animals (Figs. 4 and 5). These findings imply that the M1 projection to the cerebellar vermis is concerned more with the control of proximal and axial body movements than with the control of distal limb movements.

Origin from Regions of the SMA, CMAr, and CMAv. To examine the overall pattern of projections from the SMA, CMAr, and CMAv, we overlapped the maps of labeled neurons on the medial wall of the hemisphere from the seven animals with virus injections that involved lobules VB–VIIIb (Fig. 7 *Top*). We compared the distribution of the labeled neurons in these animals with maps of

Fig. 5. Origin of projections to lobule VI of the vermis (M19). See Fig. 4 for conventions.

arm and leg representation in the SMA, CMAr, and CMAv (Fig. 7 *Middle*) (see also ref. 16). Based on maps of body representation on the medial wall, the projection from the SMA, CMAr, and CMAv to the vermis originates from regions of arm and leg representation in each cortical area (Fig. 7 *Top* and *Middle*).

We also compared the location of neurons on the medial wall labeled by virus transport from the vermis (Fig. 7 *Top*) with the location of corticospinal neurons on the medial wall labeled in our prior studies by transport of conventional tracers from upper and lower segments of the cervical spinal cord (Fig. 7 *Bottom*) (12). Regions containing large numbers of corticospinal neurons that project to upper segments mark the location of proximal forelimb representation, whereas regions containing large numbers of neurons that project to lower cervical segments mark the location of more distal representation (12). Based on this comparison, the vermis receives equally dense projections from regions of proximal and distal representation in the CMAr and CMAv (Fig. 7 *Top* and *Bottom*). In contrast, the vermis receives a denser projection from the caudal and ventral region of the SMA, where the distal forelimb is represented, than from the more rostral and dorsal region of the SMA, where the proximal forelimb is represented. Overall, it is clear that the premotor areas on the medial wall of the hemisphere provide the vermis with a major source of input about the control of distal as well as proximal musculature.

Discussion

We would like to emphasize three major findings from the present study. First, we provide evidence that a portion of the cere-

send the vermis signals related to force, speed, and direction of motor output at the time of movement execution (20). Neurons in the SMA, CMAd, and CMAv are likely to send the vermis signals related not only to the kinematics of motor output but also to earlier stages in movement processing (21–24). The signals from the SMA, CMAd, and CMAv will arrive at the vermis during the period of motor preparation, before movement onset, as well as during movement execution. Thus the outputs from the cortical motor areas are likely to provide the vermis with information about the motor commands associated with the preparation for and performance of limb and body movements.

The output of lobules VB–VIIIb is directed largely at the fastigial nucleus. A component of the output from the fastigial nucleus is directed at regions of the thalamus that may influence the same cortical areas that provide input to the vermis (25, 26). However, the major output of the fastigial nucleus is to brainstem nuclei that are the origin of descending pathways to the spinal cord (27). Multiple lines of evidence suggest that the descending component of fastigial output is involved in the control of whole-body posture and locomotion (2–4).

We believe that the input–output organization of the projection from the cortical motor areas to the vermis is precisely what would be required to trigger and modify adaptively the anticipatory postural adjustments that are associated with limb movements (28). In essence, the control of posture is not limited to responding to external disturbances but also occurs during voluntary movement. The forces generated by normal movements are large enough to cause perturbations in posture. To prevent such perturbations and to provide a stable base of support, anticipatory postural adjustments precede and accompany movement. These adjustments result from internal commands, are adaptable, and are strongly influenced by task demands (29). Signals from the SMA, CMAd, and CMAv during the period of motor preparation could provide the vermis with information about upcoming movements. This information would be essential for the generation of the anticipatory component of postural responses. The timing of anticipatory postural adjustments could be linked to early signals from the cortical motor areas at the time of movement execution. The specific role of the vermis could be to provide the adaptive plasticity necessary to modify anticipatory adjustments for the full range of motor outputs. This speculation is supported by the finding that lesions of the cortical motor areas disrupt anticipatory postural adjustments (30), and cerebellar lesions abolish their plasticity (31).

If our speculation about the function of the input to lobules VB–VIIIb of the vermis is correct, it may provide some insight into the basis of a common disorder of movement, dystonia, which recently has been associated with dysfunction of the vermis. Dystonia is a heterogeneous, involuntary movement disorder that is characterized by excessive activation of muscle groups. The overactivation leads to the development of unusual, twisting movements and abnormal postures that generally begin and/or worsen with attempted movement (32). Some have argued that dystonia is an expression of abnormal postural control mechanisms (33). Although dystonia generally is considered to be caused by dysfunction of the basal ganglia, there is increasing evidence that the cortical motor areas and the vermis of the cerebellum contribute to the genesis and maintenance of some forms of this disorder (34). Based on our findings, an abnormal signal from the cortical motor areas, an abnormal vermal response to this input, or a combination of the two could lead to a form of “action” dystonia in which attempted movement would be accompanied by excessive anticipatory postural responses. This mechanism would explain the “overflow” seen when attempted movement results in dystonic postures in body regions apparently unrelated to the intended movement (32).

In summary, our results indicate that the vermis no longer should be considered as entirely isolated from the cerebral cortex. Instead, lobules VB–VIIIb, at least, represent a site where the cortical motor areas can influence descending control systems

involved in the regulation of whole-body posture and locomotion. Whether additional areas of the cerebral cortex, including non-motor areas in the frontal lobe, influence the function of other regions of the vermis remains to be determined.

Materials and Methods

This report is based on observations from seven macaques (*Macaque mulatta* and *fascicularis*, 2.3–9.6 kg, three males and four females). In each monkey, we injected a mixture of RV and a conventional tracer (CTb) into selected lobules of the cerebellar vermis. We coinjected CTb with RV to facilitate identification of the injection site. The protocol for these experiments was approved by appropriate Institutional Animal Care and Use and Biosafety Committees. Biosafety practices conformed to Biosafety Level 2 regulations outlined in *Biosafety in Microbiological and Biomedical Laboratories* (US Department of Health and Human Services publication No. 93–8395). Details of the procedures for handling virus and virus-infected animals have been published previously (35).

Surgical Preparation. All surgical procedures were performed under deep general anesthesia (1.5–2.5% isoflurane) using aseptic conditions. The night before surgery, the monkeys were administered dexamethasone (0.5 mg/kg, i.m.). Respiratory rate, blood oxygen level, body temperature, venous blood gas, serum electrolytes, glucose, and sensitivity to noxious stimuli were monitored at regular intervals during the procedure.

Cerebellar Vermis Injections. Each monkey's head was restrained in a Kopf stereotactic frame (Kopf Instruments). We made a craniotomy to expose the posterior vermis and the paramedian lobules of the cerebellum. Prior structural MRIs of each cerebellum enabled define the angle of approach and the depth of injections into the vermis. We used a Hamilton syringe with a 30-gauge needle to inject a mixture of RV (N2c strain, 4.5×10^9 pfu/mL; provided by M. Schnell, Thomas Jefferson University, Philadelphia, PA) and CTb (0.02%; List Biological Laboratories). Small amounts of the mixture (0.2 μ L) were injected at 0.5-mm intervals along needle penetrations into the cerebellum. The cerebellar fissures in the posterior vermis can extend more than 9 mm below the surface. As a consequence, substantial portions of the vermis are buried within these fissures. To reach the full depths of vermal folia with angled penetrations, we injected up to 15 mm below the cerebellar surface. In six of the seven animals, we injected tracer at multiple locations in the posterior vermis by inserting the injection needle at six to eight sites. In one animal, we injected tracer at multiple locations in the posterior vermis by varying the angle of each needle penetration made at a single entry site. When we completed the injections, we covered the cerebellum with artificial dura, closed the incision in anatomical layers, and gave an analgesic (buprenorphine) and an antibiotic (ceftriaxone) at the appropriate intervals.

Prior studies have demonstrated that RV is transported exclusively in the retrograde direction in a time-dependent fashion. The time to infect first-, second-, and third-order neurons depends on the strain of RV and its concentration. Based on prior results (5, 7), we set the survival time following the cerebellar injections to 42 h. This interval is sufficient to allow transport of the N2c strain to second-, but not third-order neurons.

Histological Procedures. At the end of the survival time, each animal was deeply anesthetized (ketamine, 20–25 mg/kg, i.m. followed by sodium pentobarbital, 40 mg/kg, i.p.) and was perfused transcardially with a three-step procedure. The perfusates included (i) 0.1 M phosphate buffer; (ii) 10% buffered formalin; and (iii) 10% buffered formalin with 10% glycerol added. We separated the brain into a cerebellar and a cerebral cortical block and stored the blocks at 4 °C in buffered 10% formalin with 20% glycerol for 5–7 d. The cerebral cortical block extended from the frontal pole to at least 2 mm beyond the posterior extent of the central sulcus. We cut serial 50- μ m frozen sections in the sagittal plane of the cerebellar block and in the coronal plane of the cerebral cortical block. Every tenth section was stained with cresyl violet to reveal cytoarchitecture. To identify virus-infected neurons, we processed at least every fourth section of the cerebral cortex as free-floating tissue according to the avidin-biotin peroxidase method (Vectastain; Vector Laboratories). Rabies antigen was detected using a monoclonal antibody directed against the rabies virus phosphoprotein (M957, diluted 1:300) (supplied by A. Wandeler, Animal Diseases Research Institute, Ottawa, ON, Canada). To identify the injection sites, we processed every fourth section of the cerebellum, as described above, to detect rabies antigen. We also processed another set of free-floating sections (every fourth section) using the avidin-biotin peroxidase method and goat anti-cholera toxin (diluted

1:10,000; List Biological Laboratories) to detect CTb. Reacted tissue sections were mounted on gelatin-coated glass slides, air dried, and coverslipped.

Analytic Procedures. We used an Olympus BX51 microscope, (40, 100, and 200 $\times$ magnification) and bright-field illumination to determine the spread of tracers at injection sites in the vermis and the location of virus-infected neurons in the cerebral cortex. We plotted the results of this analysis using a computer-based charting system (MD2; AccuStage). The system is based on linear optical encoders that are coupled to X–Y movements of the microscope stage.

Injection Sites. We confirmed the sites of entry of the injection needle on the fixed cerebellum (Fig. 1) and on histological sections. Throughout the text we use the nomenclature of Madigan and Carpenter (36) to describe the lobules and fissures of the vermis. To define the spread of tracer, we plotted the location of CTb staining in every fourth section through the vermis. To analyze the full extent of tracer spread, we created unfolded maps of the cerebellar vermis from the charts of single sections using software generated in the laboratory (Fig. 2). This analysis confirmed that all injections were confined to the vermis.

Cortical Labeling. We plotted the location of RV-labeled neurons in every fourth section through the cerebral cortex. The plots began at the frontal pole and extended to at least 2 mm past the posterior extent of the central sulcus. Then, we used laboratory-generated software to construct maps showing the location and density of labeled neurons in the frontal lobe. The procedures used to create these maps have been described in detail previously (12). Briefly, we marked major morphological features (e.g., surface and depths of sulci) on each charted section and drew the border between

the cerebral cortex and white matter. The computer program used this information along with the location of labeled neurons to create flattened maps from regions of the cerebral cortex. To examine the density of labeled neurons, the computer program divided labeled regions into 200- or 400- μ m bins, counted the number of labeled neurons in each bin, and color-coded the result for display.

Composite Maps of Cortical Labeling. We overlapped the flattened maps of labeled neurons from individual animals using the map of animal M18 as the template. We selected animal M18 because (i) sections in this animal included the full rostro-caudal extent of the cingulate sulcus, and (ii) the pattern of sulci in animal M18 was typical of macaques. We aligned each of the maps on the medial edge of the hemisphere and warped each map to that of animal M18. The warping procedure involved an overall scale adjustment followed by a section-by-section adjustment along the medio-lateral axis using landmarks in individual sections to guide the match to sections of the template. The maps of individual animals were rebinned after warping. Then the number of labeled neurons in each of the bins was added to the corresponding bins in a composite map and color-coded for display.

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